ADVANCING MULTIPLE SCLEROSIS TREATMENT: UNVEILING PROMISING THERAPEUTIC TARGETS AND THE INTEGRAL ROLE OF MEDICAL REHABILITATION-REVIEW WITH DATA FROM THE LITERATURE

CODREANU BALABAN RAMONA ANDREEA [1] [2], MUJA LAVINIA FLORENTA [1] [2], GACHE ALEXANDRA-CRISTIANA[3], VRANAU DIANA MARINA [1], MIHALE IULIANA [1], DOCU AXELERAD SILVIU[4], AXELERAD ANY[1] [2]

Abstract:

Aim. Multiple sclerosis (MS) is characterized by an autoimmune response that affects the central nervous system, leading to significant disability and posing a substantial burden on healthcare systems. The management of MS has made significant progress in the last thirty years, primarily through the introduction of new disease-modifying therapies that target various mechanisms such as immune modulation, immune cell suppression or depletion, and enhanced immune cell sequestration.

The most recent immunotherapies available for multiple sclerosis (such as fingolimod, natalizumab, dimethyl fumarate, teriflunomide, and alemtuzumab) offer improved efficacy or tolerability compared to injectable therapies used in the 1990s. However, they also entail higher risks. With the emergence of additional treatments (such as daclizumab and ocrelizumab), doctors must navigate through a complex range of medications and choose a specific treatment strategy, which may involve an "escalation" or "induction" approach.

During treatment, both neurologists and patients need to remain vigilant for signs of disease breakthrough or adverse effects.

Keywords: multiple sclerosis, treatment, immunotherapies, patients.

Introduction:

Multiple sclerosis (MS) is the most prevalent autoimmune condition that affects the central nervous system (CNS), with a prevalence of over 900,000 individuals in the United States and over 2 million people worldwide. (Wallin MT, Culpepper WJ, Campbell JD, Nelson LM, Langer-Gould A, Marrie RA, et al., 2019; GBD 2015 Neurological Disorders Collaborator Group, 2015).

Epidemiologically, multiple sclerosis (MS) is a diverse condition influenced by a combination of genetic and environmental factors. Genetic factors play a role, such as the association with the HLA-DRB1*15:01 genetic variant. Environmental factors also contribute to the risk and development of MS, including vitamin D levels, obesity, smoking, and Epstein Barr virus (EBV) infection (Ascherio A, Munger KL., 2016; Reich DS, Lucchinetti CF, Calabresi PA, 2018).

The diagnosis of multiple sclerosis (MS) involves the presence of a characteristic clinical syndrome, along with evidence of dissemination of lesions in space and time. The updated McDonald's criteria in 2017 allow for earlier diagnosis by considering a single clinical episode along with MRI findings showing symptomatic or asymptomatic lesions, with T1 enhancement or without T2 hyperintensity, indicative of MS. Additionally, the presence of specific oligoclonal bands in the cerebrospinal fluid (CSF) further supports the diagnosis (Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al., 2018).

The clinical classification of multiple sclerosis (MS) includes several subtypes. These subtypes consist of clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS). Each subtype represents a distinct clinical course and pattern of disease progression in individuals with MS (Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al., 2018).

Clinically isolated syndrome (CIS) is characterized by the initial occurrence of demyelination, presenting with typical symptoms of a multiple sclerosis (MS) attack, such as optic neuritis, brainstem lesions, or spinal cord lesions. However, the criteria for a definitive diagnosis of MS are not fully met at this stage. A recent update to the classification of MS subtypes,

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[1]Department of Neurology, County Clinical Emergency Hospital of Constanta, 900591 Constanta, Romania; Corresponding author: codreanuramonaandreea@gmail.com, tel. +40728574167.
[2] Department of Neurology, Faculty of General Medicine, Ovidius University, 900470 Constanta, Romania.
[3] Pneumology Resident, Clinical Pneumophtysiology Hospital of Constanta, Romania.
[4] Faculty of General Medicine and Pharmacy, "Vasile Goldis" Western University of Arad, 317046 Arad, Romania.

proposed by Lublin et al., suggests further refinement by classifying MS subtypes as "active" or "inactive" based on clinical relapse and/or MRI activity. This modification aims to provide additional insights into the progression and activity of the disease in MS patients. (Lublin FD, Reingold SC, Cohen JA, Cutter GR, Sørensen PS, Thompson AJ, et al., 2014)

There is increasing evidence that the phenotype in MS (relapsing vs progressive) is likely determined by "host factors," particularly the age of the patient, with younger patients having a higher frequency of relapses, and older patients being more likely to have progressive phenotypes. (Waubant E, Lucas R, Mowry E, Graves J, Olsson T, Alfredsson L, et al., 2019)

Material and methods:

In the review, we examined the use of state-of-the-art treatment modalities for multiple sclerosis (MS) to investigate and evaluate the efficacy of innovative therapeutic approaches using data from the literature.

These cutting-edge treatment options were chosen to address the evolving landscape of MS management and explore new strategies that hold promise for improving patient outcomes. By utilizing these advanced therapies, we aimed to shed light on their efficacy, safety, and potential impact on the course of MS, with the ultimate goal of advancing the field of MS treatment and providing new avenues for patient care.

Therapeutic goals in the management of multiple sclerosis:

Multiple sclerosis (MS) is a complex disorder of the central nervous system and the development of new therapeutic targets is a promising direction in the management of this disease. Recent research has identified a number of novel therapeutic targets in MS that have the potential to revolutionise the way we approach the treatment and management of the disease. (Scolding N, Barnes D, Cader S, Chataway J, Chaudhuri A, Coles A, et al., 2015)

Given the complexity of the treatment landscape for multiple sclerosis (MS), it has become increasingly important for physicians to have a systematic approach to categorizing disease-modifying therapies. This allows for better organization of thoughts and clear communication with patients. Instead of relying on an unstructured list of individual drugs, each treatment should be evaluated across three domains: efficacy, safety, and treatment burden, which includes factors such as mode of administration and monitoring intensity. (Scolding N, Barnes D, Cader S, Chataway J, Chaudhuri A, Coles A, et al., 2015)

In patient discussions, these categories are sometimes simplified as "low risk, low gain" and "high risk, high gain". However, not everyone agrees with this classification, as some argue that drugs like fingolimod and dimethyl fumarate should fall into a third category, given their potentially greater efficacy compared to interferon beta, as well as a potential risk of progressive multifocal leukoencephalopathy (PML) (as reported by the Food and Drug Administration). (Scolding N, Barnes D, Cader S, Chataway J, Chaudhuri A, Coles A, et al., 2015)

In 2018, both the European Committee of Treatment and Research in Multiple Sclerosis (ECTRIMS) and the European Academy of Neurology (EAN) published guidelines, along with the American Academy of Neurology (AAN), for the pharmacological treatment of individuals with multiple sclerosis (MS). These guidelines aim to provide evidence-based recommendations for healthcare professionals involved in the management of MS, helping them make informed decisions regarding treatment options for their patients. The guidelines take into account various factors such as disease subtype, disease activity, and individual patient characteristics to offer tailored recommendations for optimal patient care. (Montalban X, Gold R, Thompson AJ, Otero-Romero S, Amato MP, Chandraratna D, et al., 2018; Rae-Grant A, Day GS, Marrie RA, Rabinstein A, Cree BAC, Gronseth GS, et al., 2018)

In the case of clinically isolated syndrome (CIS), the ECTRIMS/EAN committee recommends the use of interferon or glatiramer acetate for patients with abnormal MRI findings suggestive of multiple sclerosis (MS), even if they do not meet the full diagnostic criteria for MS. However, the AAN suggests conducting annual imaging for the first five years prior to initiating disease-modifying therapies (DMTs) to screen for new disease activity. (Montalban X, Gold R, Thompson AJ, Otero-Romero S, Amato MP, Chandraratna D, et al., 2018)

For confirmed relapsing MS, the recommendations from both ECTRIMS/EAN and AAN are generally aligned with the practices followed by most MS centers. These recommendations emphasize that patients should be provided with information regarding all reasonable DMT options, taking into consideration factors such as medical co-morbidities, disease severity, specific adverse effects of medications, as well as medication adherence and accessibility. (Montalban X, Gold R, Thompson AJ, Otero-Romero S, Amato MP, Chandraratna D, et al., 2018)

The goal is to individualize the treatment approach, ensuring that patients are presented with a range of DMT options that are suitable for their unique circumstances, enabling them to make informed decisions in collaboration with their healthcare providers. (Montalban X, Gold R, Thompson AJ, Otero-Romero S, Amato MP, Chandraratna D, et al., 2018)

Although these studies cannot directly establish superiority or inferiority among the different DMTs due to inherent limitations and potential biases, they provide valuable information on the real-world effectiveness and potential benefits of individual medications. It is important for healthcare providers to consider these findings alongside other factors such as safety profile, tolerability, patient preferences, and specific clinical characteristics when making treatment decisions for their patients with relapsing MS. (Montalban X, Gold R, Thompson AJ, Otero-Romero S, Amato MP, Chandraratna D, et al., 2018)

As patients progress to the neurodegenerative stage of multiple sclerosis (MS), there is typically a decline in overall inflammatory activity. Consequently, disease-modifying therapies (DMTs) that primarily target active disease activity may become less effective over time, particularly in patients who have experienced a sustained absence of further disease activity. (Montalban X, Gold R, Thompson AJ, Otero-Romero S, Amato MP, Chandraratna D, et al., 2018)

In such cases, there are considerations for potentially discontinuing DMTs. These considerations include the increasing risks of complications from medication side effects as patients age, the presence of additional medical co-morbidities that may interact with the DMTs, and the costs and expenses associated with continuing DMT treatment. (Montalban X, Gold R, Thompson AJ, Otero-Romero S, Amato MP, Chandraratna D, et al., 2018)

Stopping DMTs should always be done in consultation with a healthcare provider who can assess the individual patient's specific situation, taking into account factors such as disease activity, the patient's overall health status, and their preferences. This decision should be carefully weighed, considering the potential benefits and risks of continued treatment versus discontinuation. (Hartung H-P, Meuth SG, Miller DM, Comi G., 2021)

It is important to note that even if DMTs are discontinued, appropriate monitoring and follow-up should still be maintained to ensure ongoing disease management and timely intervention if there are signs of disease activity recurrence. (Hartung H-P, Meuth SG, Miller DM, Comi G., 2021)

The available data on discontinuation of disease-modifying therapies (DMTs) in the later stages of multiple sclerosis (MS) primarily rely on retrospective analyses. One meta-analysis, which examined 38 clinical trials, evaluated the efficacy of DMTs in terms of disability progression using a regression model. The findings from this analysis indicated that DMTs with higher efficacy show the most significant benefits in younger patients who are in the earlier stages of the disease. However, the analysis also revealed limited benefits of these higher efficacy DMTs in patients older than 53 years. (Hartung H-P, Meuth SG, Miller DM, Comi G., 2021)

It's important to note that this meta-analysis provides insight into the general trends observed in clinical trials, but individual patient responses and circumstances can vary. The decision to discontinue DMTs in later stages of the disease should be made on a case-by-case basis, taking into consideration factors such as the patient's age, disease progression, overall health status, and preferences. Close monitoring and ongoing assessment of disease activity and treatment response are crucial when considering discontinuation. (Hartung H-P, Meuth SG, Miller DM, Comi G., 2021)

Further research, including prospective studies, is needed to gain a more comprehensive understanding of the effects and optimal timing of DMT discontinuation in older patients and those in advanced stages of MS. These studies can help guide healthcare providers in making informed decisions regarding treatment strategies in these specific populations. (Weideman AM, Tapia-Maltos MA, Johnson K, Greenwood M, Bielekova B. , 2017)

Role of medical rehabilitation in multiple sclerosis:

Multiple sclerosis (MS) management has witnessed notable enhancements owing to the effectiveness demonstrated by various rehabilitation techniques.

In the context of multiple sclerosis, neurorehabilitation has emerged as a relatively recent treatment approach, primarily employed either as a supportive therapy for symptom management or as a preventive strategy to mitigate the consequences associated with a sedentary lifestyle. (Baird, J.F.; Sandroff, B.M.; Motl, R.W., 2018; Riemenschneider, M.; Hvid, L.G.; Stenager, E.; Dalgas, U., 2018; Dalgas, U.; Langeskov-Christensen, M.; Stenager, E.; Riemenschneider, M.; Hvid, L.G. , 2019)

Research findings indicate that individuals with multiple sclerosis (MS) who participate in rehabilitation programs experience notable improvements in their quality of life and demonstrate increased independence in their daily activities. (Tollár, J.; Nagy, F.; Tóth, B.E.; Török, K.; Szita, K.; Csutorás, B.; Moizs, M.; Hortobágyi, T., 2020; Amatya, B.; Khan, F.; Galea, M. , 2019)

Multiple sclerosis (MS) gives rise to a diverse array of symptoms, which are influenced by different patterns of damage within the central nervous system, ultimately resulting in varying levels of disability. In the relapsing-remitting form of MS, visual deficiencies (46%) and sensory impairments (41%) are the most commonly observed symptoms. On the other hand, primary-progressive MS predominantly manifests with gait impairments (88%) and varying degrees of muscle weakness (38%). (Kesselring, J.; Beer, 2005)

The primary objective of rehabilitation in multiple sclerosis is to facilitate optimal recovery for patients, enabling them to minimize physical and cognitive impairments and ensuring their continued integration into society, whether partially or fully. These therapies are tailored to the individual needs of MS patients, aiming to enhance their overall well-being and functional abilities. (East Kent Hospital University NHS Foundation Trust, 2022)

Gait rehabilitation plays a crucial role in the treatment of multiple sclerosis, with the primary objective of addressing the deficits that arise due to various factors such as sensory disturbances, cerebellar impairments, spasticity, and muscle weakness. These factors significantly contribute to a substantial decline in the quality of life experienced by individuals with multiple sclerosis. (Heesen, C.; Böhm, J.; Reich, C.; Kasper, J.; Goebel, M.; Gold, S.M., 2008)

Multiple sclerosis patients have been subjected to various neurorehabilitation strategies aimed at enhancing balance and coordination. Presently, several tests are utilized to monitor various static and dynamic parameters that influence these functions. Clinical settings commonly employ tests such as the Trunk Impairment Scale (TIS), Berg Balance Scale (BBS), International Cooperative Ataxia Rating Scale (ICARS), and Nine-Hole Peg Test (NHPT). The TIS is a dependable evaluation tool specifically designed for multiple sclerosis patients, assessing three key parameters: coordination, static sitting balance, and dynamic sitting balance. (Verheyden, G.; Nuyens, G.; Nieuwboer, A.; Van Asch, P.; Ketelaer, P.; De Weerdt, W., 2006)

The International Cooperative Ataxia Rating Scale (ICARS) is a validated and reliable scale used to assess ataxia, which is a common symptom in multiple sclerosis. The scale comprises four subscales that specifically address various aspects related to ataxia, including posture and gait disorders, limb ataxia, dysarthria (speech impairment), and oculomotor (eye movement) impairments. The ICARS provides a comprehensive evaluation of these domains, aiding in the assessment and monitoring of ataxia in individuals with multiple sclerosis. (Salcı, Y.; Fil, A.; Keklicek, H.; Çetin, B.; Armutlu, K.; Dolgun, A.; Tuncer, A.; Karabudak, R.)

The advancement of technology has brought about new opportunities in the field of neurorehabilitation, offering possibilities for treatment, diagnosis, and progress monitoring. Virtual reality devices have gained significant attention in various sectors, including healthcare, since their mass production began in the 1990s. This technology has shown potential in revolutionizing neurorehabilitation by providing immersive and interactive experiences that can enhance therapeutic interventions for individuals with neurological conditions such as multiple sclerosis. (Verdict. History of Virtual Reality: Timeline, f.a.).

Discussions:

In comparison to the information provided in the article "Therapeutic Advances in Multiple Sclerosis" published in Frontiers in Neurology, June 2022, there are several similarities and overlaps in the content. (Frontiers in Neurology, 2022)

Both sources discuss the significant progress made in the management of multiple sclerosis (MS) over the past few decades through the introduction of new disease-modifying therapies. They emphasize the importance of personalized treatment approaches based on disease subtype, disease activity, and individual patient characteristics.

The article in Frontiers in Neurology explores therapeutic advances in multiple sclerosis, focusing on innovative treatment approaches and their efficacy, safety, and impact on patient outcomes. It delves into specific immunotherapies such as fingolimod, natalizumab, dimethyl fumarate, teriflunomide, and alemtuzumab, highlighting their improved efficacy or tolerability compared to older injectable therapies.

Similarly, the discussion in the previous text highlights the newer immunotherapies available for multiple sclerosis, including fingolimod, natalizumab, dimethyl fumarate, teriflunomide, and alemtuzumab. It also mentions the categorization of disease-modifying therapies based on their efficacy, safety, and treatment burden.

Both sources touch upon the complexity of managing MS, the decline in inflammatory activity in the neurodegenerative stage of the disease, and the considerations for discontinuing disease-modifying therapies in later stages. They acknowledge the limitations of retrospective analyses and the need for further research, including prospective studies, to gain a better understanding of treatment outcomes and optimal strategies for advanced stages of MS. However, it is important to note that the previous text is a compilation of paraphrased statements and information from multiple sources, while the article in Frontiers in Neurology is a comprehensive review specifically focused on therapeutic advances in multiple sclerosis. The article provides a more detailed analysis of the topic, incorporates additional research findings, and provides a structured and evidence-based review of the subject matter.

In comparison to the article "Neurorehabilitation in Multiple Sclerosis—A Review of Present Approaches and Future Considerations" published in the Journal of Clinical Medicine in 2022, there are notable similarities and connections in the content. (Journal of Clinical Medicine, f.a.)

Both sources emphasize the importance of neurorehabilitation in the management of multiple sclerosis (MS) and highlight the need for tailored approaches to address the diverse symptoms and challenges faced by MS patients. They acknowledge that neurorehabilitation plays a crucial role in improving quality of life and promoting independence for individuals with MS.

In summary, the previous text and the article "Neurorehabilitation in Multiple Sclerosis—A Review of Present Approaches and Future Considerations" published in the Journal of Clinical Medicine highlight the significance of neurorehabilitation in managing multiple sclerosis (MS) and discuss current approaches and future considerations.

While the previous text provides a broader overview of neurorehabilitation and its role in MS management, the article in the Journal of Clinical Medicine offers a specialized and comprehensive review. It delves into specific neurorehabilitation strategies, such as physical therapy, occupational therapy, speech therapy, and cognitive rehabilitation, providing in-depth analysis and research findings. The article also discusses emerging technologies and future directions in the field of neurorehabilitation.

Together, these sources emphasize the importance of personalized neurorehabilitation approaches in addressing the diverse symptoms and challenges faced by individuals with MS. They highlight the need for ongoing research, standardized protocols, and advancements in technology to optimize neurorehabilitation interventions and improve outcomes for MS patients.

Conclusions:

In conclusion, the management of multiple sclerosis (MS) has witnessed significant advancements with the introduction of new disease-modifying therapies targeting various mechanisms. These therapies have shown improved efficacy and tolerability compared to previous treatments, but they also come with increased risks that need to be carefully evaluated on an individual basis. As patients progress to the neurodegenerative stages of MS, the effectiveness of therapies targeting inflammation may decrease, and decisions regarding therapy discontinuation should be carefully considered based on the risks and benefits for the patient.

Neurorehabilitation plays a crucial role in managing MS symptoms, but there is a need for ongoing updates and research to determine the most effective therapeutic approaches. Improvements in study designs and the evaluation of tests used for assessing disease status and treatment efficacy are necessary to reduce biases and improve accuracy. International collaboration can help establish standardized protocols for exercise programs and physiotherapeutic approaches that have been rigorously tested and approved. Technological innovation holds promise in tracking treatment responses more accurately and introducing novel therapeutic solutions in the field of rehabilitation.

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