Therapeutic strategies for multiple sclerosis: Current data

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ABSTRACT

At present, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved drugs for Relapsing Remitting Multiple Sclerosis (RRMS) and Secondary Progressive MS (SPMS). In this paper, modern therapeutic strategies for MS are reviewed. A comprehensive research in MEDLINE, PUBMED, and SCIENCEDIRECT databases using two Boolean phrases {i.e. 1. [(Multiple Sclerosis) and (Disease Modifying Therapies)] and 2. [(Multiple Sclerosis) and (Neuroprotective Therapies)]} yielded more than 1,5000 articles in total. Therefore, for the purposes of this paper, articles written within the last decade were considered for review.

Key words: Disease-modifying therapies, multiple sclerosis, neuroprotective strategies

INTRODUCTION

Multiple sclerosis (MS) is an unwelcome visitor in people's lives. It represents a clinically impactful disorder, especially given its detrimental effects on functioning. The disease undermines personal and professional activities even in early disease stages.[1] The magnitude of the problem is also reflected by the emotional, mental, and physical stress put on families and friends of individuals who suffer from the disease. The worldwide prevalence of MS is 50 per 100,000 individuals.[2] The disease strikes mostly younger individuals.[3,4] and women are affected more frequently than men.[5] Both adults and children can be affected and present with similar clinical symptoms.[6] Nevertheless, only 3–5% of all MS cases appear during childhood.[7] This percentage might be even lower as it is argued that in some childhood MS cases, children are eventually diagnosed with acute disseminated encephalomyelitis (ADEM) instead of MS.[8] MS is classified into four types, i.e. Relapsing-Remitting MS (RRMS), Secondary-Progressive MS (SPMS), Primary-Progressive MS (PPMS), and Progressive-Relapsing MS (PRMS). The clinical course of the disease in each MS type is depicted in [Figure 1].

Currently, there is no cure for MS and interventions focus on strategies targeting treatment of MS attacks, management of symptoms, and decrease of the progress of the disease.

In this paper, current therapeutic strategies for MS are reviewed. A comprehensive research in MEDLINE, PUBMED, and SCIENCEDIRECT databases using two Boolean phrases {i.e. 1. [(Multiple Sclerosis) and (Disease Modifying Therapies)] and 2. [(Multiple Sclerosis) and (Neuroprotective Therapies)]} yielded more than 15,000 articles in total. Therefore, for the purposes of this paper, articles written within the last decade were considered for review. This paper is a critical appraisal of current research in the field of MS therapeutics and not a systematic review.

REVIEW OF CURRENT DATA

The complexity of MS pathophysiology and its role in disability

MS is currently considered a demyelinating and neurodegenerative condition.[9,10] The pathogenesis of brain damage is extremely complex and differs between early and late stages of MS.[11] Currently, it is believed that inflammation predominates in early stages of MS,[12,11] whereas neurodegeneration holds sway in later stages and is correlated with worsening clinical disability.[12-14] Axonal

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damage in late stages, despite low levels of inflammation, might be explained by age-related accumulation of iron and former oxidative injury.[11] It is also suggested that some irreversible axonal damage can occur in very early stages of MS, but due to neuroplasticity, gross clinical disability appears much later.

Currently, there is a debate regarding the relationship and interaction between inflammation and neurodegeneration in MS, and this is one of the reasons that has shifted our focus from disease modifying treatments (DMTs) to neuroprotective interventions. A large body of research suggests that axonal damage occurs in the absence of demyelinating processes.[15-18] What is more, there is evidence that neurodegeneration might be the primary pathological process observed in MS.[19,20] On the contrary, many researchers consider axonal degeneration as a consequence of demyelination.[15] In this context, it is believed that there exists a substantial association between inflammation and degeneration in the clinical course of MS,[15,16] and neuropathological findings suggest that inflammation is the cause of axonal degeneration.[17] The debate is still ongoing and, therefore, the degree to which axonal loss is the result of inflammation is yet to be determined.[21] Table 1 summarizes current views on the pathophysiological mechanisms that are responsible for demyelination and neurodegeneration.

As it is currently accepted that MS disability is related to inflammation-neurodegeneration complexity, measuring the pathophysiological features that reflect various stages of inflammation and axonal degeneration and unraveling the exact patterns/mechanisms of inflammation and neurodegeneration may result in a return to complete health and not just resolution of symptoms.

REVIEW OF CURRENT INTERVENTIONS

At present, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved therapies for RRMS and SPMS.[28] Even though modern therapy focuses on progressive MS types;[29] so far, therapies for PPMS do not exist.[28] Current approved, off-label, and emerging therapies are summarized in Table 2.

Off-label agents are given either to those who cannot tolerate the approved drugs or else to those who follow intense therapies.[28] Such therapies are linked to more severe and systemic side effects (e.g. high risk for cancer, opportunistic infections) and limitation to their regular use is attributable both to severe side effects and lack of

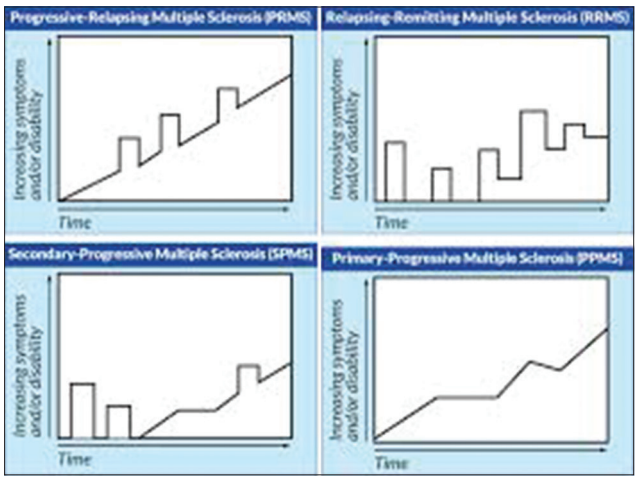

Figure 1: Clinical course of each MS type

Table 1: Pathophysiology of demyelination and axonal loss

Demyelination	Neurodegeneration
B-cells, T-cells, microglia, macrophages and plasma cells are associated with demyelination[16,22]	B-cells, T-cells, microglia, macrophages, and plasma cells are associated with axonal loss[16,22]
In active lesions, CD8+T cells and macrophages (that digest degraded myelin) predominate[23]	Oxidative damage contributes to axonal loss[26]
Dysregulation of CD4 and CD25 cells leads to unhindered expansion of T cells and this is related to demyelination[24]	Axonal loss is also attributed to maladaptive processes (e.g., sodium and calcium channelopathies, suppression of mitochondrial function leading to depletion of energy to demyelinated neuroaxons)[23]
Astrocytes are also affected within the lesions[25]	Excessive glutamate and increased nitric oxide may have detrimental effects on axons[23]
Oxidative damage also contributes to demyelination[26]	Plasma cells accumulate in later stages in the central nervous system CNS[16]
Early MS lesions are caused by apoptosis of oligodendrocytes with minimal microglial and astocytic contribution[23]	Plasma infiltrates correspond mostly to PPMS and SPMS[16]
At very late stages of MS, inflammation may decrease to levels seen in controls[16]	Even though SPMS patients present with higher levels of inflammation compared to PPMS patients, PPMS patients present with higher levels of axonal loss PPMS[27]
	Neurodegeneration decreases in severity with age increase and disease duration[16]

MS: Multiple sclerosis, CNS: Central nervous system, PPMS: Primary progressive multiple sclerosis, and SPMS: Secondary progressive multiple sclerosis

Table 2: Current approved, off-label, and emerging therapies

Current approved	Off-label	Emerging therapies
INF-β1a (Avonex)	Mycophenolate mofetil	Laquinimod
INF-β1a (Rebif)	Azathioprine	Teriflunomide
INF-β1b	Methotrexate	Dimethyl fumarate (BG-12)
(Betaseron/ Betaferon/Extavia)	Rituximab	Alemtuzumab
Glatiramer acetate (Copaxone)	Immunoglobulin	Daclizumab
Mitoxantrone	Corticosteroids	Ocrelizumab
Natalizumab (Tysabri)		
Fingolimod		

INF: Interferon

large scale randomized control trials (RCTs).[28] Approved and emerging agents also present with sometimes severe, side effects (e.g. skin reactions and cancer, liver enzymes abnormalities, depression, fatigue, diarrhea, thyroid disturbance, cardiotoxicity, etc.).[28] Side effects are the price that patients have to pay in their attempts to tame nature and depict the power and complexity of human nature. This is why balancing benefits and risks is a very responsible procedure and demands active participation and involvement of patients (autonomy) in decision-making processes.

Disease modifying therapies

During the last 20 years, among all neurological diseases, MS is linked to the biggest progress in treatment.[30] Since the advent of DMTs in 1993, the natural course of the disease has significantly changed.[31,32] But this is only true for the relapsing type of MS.[29] What is more, DMTs do not work for some people and also many patients exhibit severe adverse effects.[33] This is why there is an imperative need for molecular biomarkers predicting either the benefit or else poor response to DMTs. In addition, the rationale behind the use of DMTs for MS is not well-documented for many current drugs since the mechanisms that underlie the clinical effects of some agents have not yet fully unraveled. This is the case for basic licensed agents, such as Interferons (INFs), Glatiramer (GA) and for some experimental drugs as well (e.g. teriflunomide, dimethyl fumurate).[29] Also, the impact of some agents (e.g. natalizumab) on long-term disability is yet to be founded.[29]

INFs have anti-inflammatory effects[34] and together with GA, which also have anti-inflammatory properties, must be considered first line in newly diagnosed MS.[28] As for fingolimod, several animal studies have shown that it can reduce demyelination and boost remyelination.[35] Fingolimod is the first oral disease modified drug (DMD) suggested for people who either do not respond to first-line agents, or else present with more aggressive MS at onset.[28] Phase III clinical trials in humans show that fingolimod may reduce brain atrophy and currently, results are awaited from related ongoing research in PPMS.[35] Also, it has been supported that it is an encouraging therapy that may prove to have neurobiological effects.[36] Mitoxantrone is an immunosuppressive agent used as a second line drug for SPMS, PRMS, and worsening RRMS.[28] There is evidence that mitoxantrone suppresses humoral immunity, but its use is restricted due to a) scarcity of clinical trials and b) its potential toxic effects.[37] In one study, both safety and efficacy of mitoxantrone were assessed retrospectively in 19 pediatric patients with aggressive MS and it was found that this agent may suppress effectively worsening RRMS and SPMS.[38] Even though the sample was small, and this was acknowledged by the researchers, such preliminary data urge scientists to further examine the efficacy and safety of this drug. Natalizumab is also suggested for people who do not respond to first-line agents, or present with more aggressive MS at onset,[28] and it is suggested that even though it may provoke multifocal leukoencephalophaty (PML)—and this is a serious concern—it is highly efficacious for RRMS.[37] Another study analyzed safety and efficacy profiles of natalizumab in MS patients under 18 years old and found that it be used as a highly effective second-line drug.[39]

As for emerging therapies, teriflunomide, that has been recently approved, seems to be a good treatment option for RRMS,[40] but might also have hepatotoxic and teragogenic effects.[41] Alemtuzumab has shown efficacy in phase III clinical trials, but due to its severe side effects it needs monitoring.[37] Daclizumab and ocrelizumab are both currently being tested in ongoing phase III trials and ofatumumab is being tested in phase II trials.[37]

At present, there are no approved agents in the market for PPMS[28] and SPMS[42] and this is devastating for both the physical and mental health of MS patients. In these progressive MS types, symptomatic therapies are applied.[32] Recently, it was supported that interventions for PPMS mostly fail because they focus on peripheral immune system derangement (which is likely to be the minor cause of axonal damage).[29] A better understanding of the pathophysiology of this MS subtype may guide treatment.

Current approved treatments target inflammation[12] and even they are currently used effectively in reducing relapses, their properties regarding prevention of neurodegeneration and subsequent disability are poor.[43] But, it is suggested that during active disease, the extent of inflammation correlates with neurodegeneration.[14] So, it is reasonable to think that

fighting against inflammation may prove to be beneficial for protection of neurons. Even though it has been alleged that some agents (i.e. GA) may have anti-neurodegeneration properties,[44] other researchers support that there is no clinical evidence that anti-inflammatory therapies also have neuroprotective properties.[45]

NEUROPROTECTIVE STRATEGIES

The notion of neuroprotection is very broad and includes the preservation of the integrity of neurons (myelin included) and glial cells.[29] As it is now well-known that MS causes neural axon loss, it is common sense to say that there is an imperative need for therapies targeting inhibition of neurodegeneration, promotion of neuronal repair and remyelination. This is particularly important as the prognosis regarding recovery is poor if effective treatment is started after substantial neural loss.[32]

Even though it has been recently supported that future therapies should target both inflammation and axonal loss,[15] it is currently argued that primary neuroprotection should be achieved outside immune modulation because axonal damage may happen even in the absence of active inflammation.[21] In any case, valid and responsive biomarkers of axonal integrity that are a prerequisite for testing the effectiveness and neuroprotective therapies are not currently available.[23]

Development of neuroprotective therapies requires well-designed double blind RCTs. Currently, since there is evidence supporting that inflammation in MS causes axonal damage and as we now have immunomodulatory agents, it would be unethical to deprive patients from effective anti-inflammatory therapies. Such tactic would have deleterious effects on patients and would violate the most important ethical principles, i.e. beneficence and non-maleficence. Truly, many countries forbid placebos in phase III clinical trials because there now exist efficacious treatments.[46] Instead of placebo agents, active comparators are currently used in many clinical trials, but this impacts the statistical significance of results. Employing "effect size," however, helps to quantify the effectiveness (vs. efficacy) of treatments. Unfortunately, the application of effect sizes is mostly limited to meta-analyses.

On the other side, it could be argued that neuroprotective therapies might be tested in patients with PPMS. This is because in this cohort of patients, anti-inflammatory and immunomodulatory therapies have minor or no impact on disability and axonal loss.[16]

Clinical trials focusing on neuroprotection are small in number.[23] In a 5-year period study, the impact of INF-b and GA on brain volume loss was investigated, and it was found that therapy reduces the rate of brain volume loss.[47] Postponing progression and slowing down brain damage is very crucial at a time when efforts toward neuroprotection are on the way. Furthermore, apart from the initial inflammatory cascades that cause degeneration, axonal loss is also attributed to maladaptive processes (e.g. sodium and calcium channelopathies, suppression of mitochondrial function leading to depletion of energy to demyelinated neuroaxons).[23] Such disturbed mechanisms might give rise to neuroprotective strategies. As for mitochondrial dysfunction, it is estimated that as mitochondria-related oxidative damage happens early in MS, neuroprotective therapies should boost anti-oxidant defense mechanisms and thence prevent oxidative damage.[25] Modulation of mitochondrial dysfunction has proved to be successful in Parkinson's and Motor Neuron Disease.[42] It is suggested that treating mitochondrial dysregulation and inhibiting the mechanisms of microglia and macrophages should be among modern therapeutic priorities.[42] In terms of channelopathies, it is supported that even though calcium channel blocker agents may be beneficial, they have been applied in MS without evidence for a direct neural protecitve effect.[48] Also, it is pointed out that there are studies supporting N-methyl-D-aspartate receptor (NMDA)-mediated damage may underlie neuronal damage as well and, therefore, dealing with such mechanism might help us treat the neurodegenerative aspect of the disease.[49] Neurogenesis-related therapies with stem cells are also deemed to be an interesting approach.[48] In several central nervous system (CNS) disease models, mesenchymal stem cells have shown strong anti-inflammatory, immunomodulatory, and proregenerative properties.[50] Currently, there are such ongoing clinical trials in humans and some preliminary data report promising results.[12] For example, intrathecal mesenchymal stem cell therapy was performed in 25 patients, and it was found that the immunomodulatory and neurodegenerative effects of such therapy (that are exerted locally in the CNS) may improve or stabilize the clinical course of MS.[51] Even though the sample all was small and therefore results cannot be generalized, the results are promising and further studies examining the impact of intrathecal and/or injected mesenchymal stem cells may confirm this argument. Furthermore, cannabinoids, lamotrigine, and statins are being tested for potential reparative properties.[52] Also, it is suggested that there is evidence supporting that both T cells and macrophages may promote neural reparation and survival.[52,20] If it is true that demyelination is the major

cause of neural damage, a logical mind would think that treatment should focus on remyelination. To some extent, this happens due to innate CNS neuroplasticity[52] and this shows the indispensable need for restoration of myelin. Nevertheless, if inflammation can promote reparation, this is something that further complicates algorithms for anti-neurodegenerative therapies.

At present, even though therapeutic development is accelerating, the lack of RCTs in pediatric MS does not allow progression toward the best effective therapeutic schemas in children. Therefore, well designed RCTs focusing on childhood neuroprotection are also needed.[53]

CONCLUSIONS

Before the advent of DMTs, there was no hope for MS patients. Even if DMTs are not a cure, they can modify the clinical course of the disease and this is a very important achievement for both physical and mental health of many patients. Therefore, from the perspective of patients who benefit from DMTs, neurologists have not been pursuing the wrong therapeutic strategies. Nevertheless, complete treatment is the goal and this can be achieved through management of both inflammation and neurodegeneration. It seems that at present researchers focus on the source of chronic clinical disability (i.e. neurodegeneration) and this is a promising pathway.

The need for individualized therapy is depicted in both heterogeneity and growing number of MS therapeutic options. The immunopathological heterogeneity of MS will guide treatment, but this cannot be achieved unless cerebrospinal fluid (CSF) or blood biomarkers of MS diversity are defined.[54] Current research focuses on investigation of MS biomarkers.

Assessing the benefit to risk ratio is very important when deciding on specific therapies. Benefits include decrease in disease and progression, freedom from disease, quality of life (QoL), cognition, and cost-effectiveness.[55] Apart from DMTs and neuroprotective therapies, symptom management is very crucial because it may improve the QoL and well-being of MS patients.[31] Even though symptomatic MS treatment and rehabilitation are effective,[56] only few patients receive appropriate therapy for their symptoms.[57] Also, even though the effectiveness of complementary and alternative medicine (CAM) in MS is not well-understood, a high percentage of MS patients use it.[4,58] This depicts the importance of CAM for patients and should be taken into consideration since CAM may be proved to be important in terms of dealing with MS.[4] Neuroprotective, DMTs, and Symptomatic Therapies are all necessary and important for MS patients, who are always willing to try new ""promising"" drugs, notwithstanding the, sometimes, predictable dire side effects. As scientists, we have to reciprocate the trust that our patients place in us.

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