Multiple sclerosis (MS) is an immune-mediated demyelinating disease of the central nervous system (CNS) with variable clinical manifestation and temporal course. Relapses and progression are the two characteristic clinical features in MS. Progressive disease onset is the strongest determinant of poor prognosis in MS and insufficient recovery from relapses leads to stepwise disability accumulation. Extensive evidence shows that MS is mainly a subclinical process especially early in its course, accompanied by changes in the architecture of brain and/or spinal cord tissue, subsequent to the clinical manifestation.

One of the prevailing concepts in MS is that inflammatory response is responsible for demyelination as shown in animal model studies, which has largely helped us to design relapse-prevention studies. However, the need for a paradigm shift in our approach to the pathogenesis of MS has become increasingly apparent. Clinicopathological correlation studies have taught us that MS is a pathologically heterogeneous disease related to the stage of lesion activity, disease phase, and clinical phenotype. At least four different pathological patterns of demyelination have been identified and these also exhibit a varying degree of remyelination. In two of these patterns myelin seems to be the primary target (with concomitant loss of 30 percent of oligodendrocytes); in the other two subtypes the disease appears to be directed against oligodendrocytes. Early oligodendrocyte injury is required prior to development of chronic demyelination in MS, although the initial event leading to oligodendrocyte injury is still unclear and may be present decades before clinical presentation.

Axonal degeneration and astroglial scarring is known to occur early in MS and can precede the onset of substantial demyelination. However, demyelination itself may result in acute axonal pathology, and this secondary injury to axons may be a result of T cell cytotoxicity or failure of neurotrophic support from death of myelinating oligodendrocytes. Axonal loss may be clinically silent during the relapsing-remitting phase of the disease, and once a threshold for axonal transection is exceeded, MS patients enter an irreversible progressive phase.

Remyelination, axonal, and synaptic plasticity have been identified as mechanisms underlying functional recovery. Early remyelination is likely important in determining the extent of recovery.

Remyelination is a complex cellular process involving an intimate interplay between oligodendrocytes, demyelinated axons and CNS-infiltrating immune cells. CNS has the capacity of spontaneous remyelination, but the new myelin is usually inappropriately thin for the corresponding axon with shorter internodes. The process of remyelination probably replicates the myelination during development, as the expression of developmental genes, such as exon 2 myelin basic protein transcripts, correlate with remyelination in MS. However, some other developmental proteins do not seem to play role in remyelination, as they do not result in acute axonal pathology.

Promising Directions in Relapse-Impact Prevention in Multiple Sclerosis

Current immunomodulatory treatments for MS are not reliable to prevent long-term disability, but future agents focusing on remyelination and axonal and neuronal repair could reverse this course.

BY MARTINA NOVOTNA, MD, MOSES RODRIGUEZ, MD, AND ORHUN H. KANTARCI, MD

Based on original natural history studies, prevention of relapses has taken the forefront of MS care. However, lack of repair and remyelination after a relapse (clinical or subclinical) seems to be the key factor in determining long-term disability accumulation in MS. With continued advances in the treatment and understanding of MS, there are many reasons to be enthusiastic about the future of neuroprotective treatments.
in the developmental myelina-
tion. Remyelination therefore
needs to be studied as a unique
and distinct process.

In principle, remyelination can
be achieved by either promoting
endogenous repair mechanisms,
by transplantation of exogenous
myelin forming cells, or by
limiting the damage to myelin-
atated cells. Besides, the principal
mechanisms of oligodendrocyte
biology and CNS remyelination
were explored in a variety of
experimental models.18-20

Animal model studies of CNS
demyelination also demon-
strated that the extent of remy-
elination decreases with disease
progression and capacity for
remyelination declines with
age, probably as a result of delayed expression of growth
factors, poor progenitor oligodendrocyte recruitment, and
derdifferentiation.21-24 Other studies suggest that damaged
axons are not being receptive to remyelination.25

Evidence from animal models suggest that remyelina-
tion of demyelinated axons can restore neurophysiologi-
cal function.26,27 These findings imply that remyelinating
strategies may also lead to reversal of neurological deficits
if applied before any permanent axonal damage ensues.
Complete myelin repair is likely achievable, as suggested by
the significant remyelination observed in early MS stages
in humans, as well as the strong remyelination observed
in noninflammatory animal models of demyelination.28,29
Therefore at least one aspect of future MS treatment strat-
egies should focus on active stimulation of remyelination
and repair.

Most recently, studies have recognized naturally occur-
rning antibodies (NAbs) directed against oligodendrocytes,
which demonstrate remarkable remyelination when used
as treatment in experimental models of demyelination.30,31
It would mark the first time in which MS therapies would
target the cells that produce the myelin sheath, in con-
trast to other known MS treatments. Importantly, how-
ever, better understanding of the molecular and genetic
mechanisms of remyelination is crucial for development
of treatment strategies to promote remyelination and
axonal repair. Moreover, recognizing the characteristics of
each MS phase and the importance of relapses in different
phases of MS will provide necessary insight for potential
treatment decisions.

PHASES AND CLINICAL PHENOTYPES
OF MULTIPLE SCLEROSIS

MS evolves from a high-risk phase to subclinical disease
to clinical disease evidence. In the MS risk phase, individuals
can potentially be identified by presence of known genetic
(DR15 positivity, or other combination MS risk genes), famil-
ial (family history of MS) and environmental (e.g., EBV expo-
sure, vitamin D deficiency, smoking) risk factors, a threshold
of which is yet to be defined precisely.32 In strict terms, these
individuals should have the risk factors but definitely no
subclinical (lesion on MRI or abnormal electrophysiology
studies) or clinical (relapses) evidence of MS.

The following two phases with sub-critical or clinical
disease evidence are relapsing-remitting and progressive
phases.33 Relapsing-remitting phase is characterized by epi-
sodic inflammatory-demyelination and remyelination, while
the pathological hallmark of progressive phase is progressive
axonal dysfunction or loss, with or without a certain level of
limited inflammation.3

Six clinical sub-phenotypes of MS are defined by the
relationship between presence of relapses and progressive
disease phase (see Figure 1 above). The high MS risk phase
evolves into radiologically isolated syndrome (RIS) when
patients develop subclinical relapses. Using a broad defini-
tion, RIS is characterized by incidentally identified white
matter lesions that are suggestive of MS in individuals who
lack clinical symptomatology associated with central ner-
vous system (CNS) demyelination, after exclusion of other
possible etiologies.34-37 These individuals, if they fulfill the
radiological criteria for MS, develop clinical symptoms of MS.
with an increasing yearly risk (30 percent in five years), especially if they have spinal cord lesions beforehand. For those individuals who only partially fulfill the radiological criteria for MS the evolution has not been studied yet.

While individuals with RIS may evolve into clinically isolated syndrome (CIS), many patients will present first time with CIS. If there is an ongoing background MRI activity fulfilling criteria for dissemination in time and space at the time of first clinical presentation, these patients are classified as MS, but to differentiate them from relapsing-remitting MS (RRMS), we prefer the term single-attack MS (SAMS). RRMS is characterized by multiple relapses (with or without ongoing MRI activity) with variable degree of recovery.

Each one of these three forms can potentially evolve into their corresponding progressive form, defined as an insidiously worsening neurological deficit lasting for more than one year. Secondary progressive MS (SPMS) evolves from RRMS, single-attack progressive MS (SAPMS) evolves from CIS and primary progressive MS (PPMS) likely evolves from RIS. SAPMS and SPMS are sometimes grouped together as bout-onset progressive MS (BOPMS).

Once patients enter the progressive phase, they can have continuing subclinical MRI activity with or without superimposed clinical relapses, which are more common in SPMS vs. SAPMS vs. PPMS patients (Figure 1). Progressive-relapsing MS, an earlier confusing term, referring either to insidiously worsening neurological deficit with ongoing relapses, or to relapsing-remitting MS with rapid stepwise decline in function, is now avoided.

TREATMENT IMPLICATIONS OF MULTIPLE SCLEROSIS PHENOTYPIC CLASSIFICATION

The original natural history studies done before the era of modern disease-modifying drugs (DMDs) confirmed that progressive phase is the key determinant of poor long-term disability in MS. Other factors known to be associated with worse long-term disability are male sex, older age at MS onset, spinal cord syndrome at MS onset, and high early relapse rate.

However, not all RRMS patients ultimately progress. Based on the study from Olmsted County, MN, 25 percent of all RRMS patients will still remain progression-free by 35 years from MS onset or by age 75. This effect is independent of DMD use and the reason for it is not clear. Possible explanation is that these patients repair better early on, which is partially supported by the Theiler’s virus model of demyelination-remyelination, showing that some strains repair better than the others and do not develop progressive disease course.

What we do know is conversion to progressive disease course in MS is an age-dependent process independent of disease duration and initial disease course. Presence (BOPMS) or absence (PPMS) of a symptomatic relapsing-remitting period preceding the onset of progressive disease course in MS therefore does not impact the age at progression onset.

Since both onset of progressive phase and onset of relapses are age-dependent, there should be a period when these phases overlap. To define this overlapping phase better, we mapped every existing BOPMS patient in the study population according the age at first relapse, age at progressive MS onset and age at last relapse. For 95 percent of these BOPMS patients, overlap age range (between MS onset and progressive MS onset) is between 27 and 47 years. This is the period when we usually treat these patients and the reason why we cannot achieve disease inactivity may be related to the fact that none of the available disease modifying treatments impacts progressive MS phase.

As expected, patients with multiple relapses before onset of progressive phase are more likely to accumulate disability than patients with single-attack (SAPMS) and patients with asymptomatic attacks (PPMS) before the onset of progressive MS.

Relapses can continue even after the onset of progressive MS and further increase and accelerate disability accumulation. Among BOPMS patients, about 14 percent will continue to have post-progression relapses. Absolute lifelong risk of relapses after progressive MS onset is a factor of age at progressive MS onset. Its is also worth noting that 95 percent of post-progression relapses occur before age 55, and 92 percent of post-progression relapses occur within the first five years after progressive MS onset.

Despite the fact that only about 14 percent of patients continue to have post-progression relapses, these patients reach EDSS 6 (needing a cane to walk) years earlier compared to patients without post-progression relapses. This suggests that relapse-recovery amount declines with age and disease duration. Among patients with progressive MS, both pre- and post-progression relapses, female sex after progressive MS onset, and patient age of greater than 50 years at progressive MS onset, were associated with shorter time to EDSS 6. Immunomodulation after onset of progressive disease course has shown an independent effect on preventing further accumulation of disability, possibly related to continuing background MRI activity in these patients. Therefore, it might be safe to assume that patients with active disease after progressive MS onset should benefit from treatment up to age 55, or within five years after progressive disease onset, whichever comes first. Active MS, at least at a clinical level, implies continued treatment. The role of ongoing MRI activity without clinical relapses after progressive MS onset is yet to be defined.
As can be seen from these examples, a precise definition of individual phase a patient is in, and the sub-phenotype they have, together with the age the patient is at, may already have important treatment implications with the existing DMD use and switch decisions.

**ACTIVE VERSUS INACTIVE MULTIPLE SCLEROSIS**

Within each phase, each individual can further be classified as having active vs. inactive MS. Active period is characterized by symptomatic (clinical relapses) or asymptomatic (MRI only) new lesion formation. Inactive period is defined as greater than one year without relapses or new MRI activity, which results in no disability worsening in patients who are in relapsing-remitting phase, while patients in progressive phase will continue to have insidious disability worsening.

In the MS risk phase, obviously all individuals would be inactive. In the case of relapsing-remitting phase there are several potential scenarios:

- In RIS, active asymptomatic MS (ongoing MRI activity) leads to increased evolution risk into symptomatic MS;
- In CIS/SAMS, active MS increases risk of conversion to RRMS;
- In CIS/SAMS/RRMS if patients demonstrate poor recovery from individual relapses, active MS will lead to stepwise disability worsening;
- In CIS/SAMS/RRMS if patients demonstrate excellent recovery from individual relapses despite active MS, there may be no disability worsening.

In the case of progressive phase despite inactive MS patients will have baseline insidious disability worsening independent of new clinical or sub-clinical lesion formation. However, since most patients at this phase would be older and have poor recovery, active MS can cause stepwise disability worsening in addition to baseline insidious disability worsening.

A study investigating how much absolute inactivity (no evidence of disease activity) is achievable in a cohort of RRMS patients longitudinally followed for seven years found that with the current treatment approaches, while approximately 45 percent of patients reached this end-point at year one, only 15 percent remained inactive by year five. However, in this study the term “progression” is not used in its proper sense of disease progression, but as a disability progression, which can result from stepwise disability worsening, insidious disability worsening, or both.

If we eliminate this rather confusing definition of progression and look purely at relapses, we can achieve a relatively sustained amount of 40 percent relapse-free patients at five years. Despite current medication approaches, albeit with room to investigate early vs. late aggressiveness, there are still about 60 percent of patients who do not achieve the relapse-freedom. Therefore decreasing relapses alone may not be enough to decrease the cumulative impact of relapses on disability accumulation.

Biologically active MS would be characterized by the following immunological steps:

1. Autoreactive lymphocytes get released from lymphatic organs to circulation due to an unknown trigger, differentiate and proliferate, and then pass through blood-CNS barrier.
2. In CNS parenchyma the cellular and humoral factors interact with myelin/oligodendrocyte-neuron/axon-astrocyte complex and lead to myelin/axon damage.
3. This insult is then counteracted with initiated and ongoing repair. This repair process seems to start during the active insult but continues during the inactive period, with varied amounts of individual level success.

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In Figure 2 (see above), we illustrate the multiple treatments working at different levels of disease process available for active MS to prevent future demyelination. However, none of these treatments act directly at the demyelinating axon to impact the degree of long-term disability. We are still lacking protective medications that would help with axonal preservation, enhance myelin repair, oligodendrocyte stimulation or neuronal sprouting.

**THE FUTURE OF MS TREATMENT AND THE IMPORTANCE OF RELAPSE-RECOVERY**

Besides the existing treatment strategies for MS, there are six future frontiers to tackle if one wishes to eliminate the disability impact of MS:
1. Prevent MS before it starts (e.g., vaccinations) during the high-risk phase.
2. Prevent clinical conversion during RIS.
3. Redefine the timing of aggressiveness of DMD use in individuals in the relapsing phase of MS to prevent relapses.
4. Design immediate (active period) and long-term (inactive period) repair strategies
5. Prevent progressive MS.
6. Slow or stop progressive MS after it starts.

These are lofty objectives that need to be set as the ultimate outcomes for any future-proof trial in MS. First of these goals is still a very hypothetical discussion. Second and third goals seem reachable by repurposing existing treatment strategies and several efforts are already underway. Sixth of these goals is of course an acute need with significant limitations due to our limited understanding of how to regenerate the nervous system. However, it is the focus of many investigations with some promising results presented recently. Ahead we will focus on the fourth and fifth goals as they interrelate in our opinion.

Since progressive MS is responsible for the majority of disability burden in MS patients, prevention of this phase sets the stage for highest yield of any of the goals set above. As also discussed above, relapses are likely to be caused by passage of activated and myelin-reactive T-cells into CNS, causing acute inflammation with associated edema. Each relapse carries a risk of irreversible myelin and axonal loss determined by the extent and duration of injury, and inherent ability to recover. Steroid-unresponsive relapses can improve with plasma exchange (PLEX) and cyclophosphamide can help with acute relapses. However, for relapse-recovery to matter, it needs to be linked to the most important determinant of long-term disability, which is the onset of progressive MS.

In a recent study we conducted, were able to demonstrate that better recovery from early (within first five years) relapses will significantly delay progressive MS onset. We found that 50 percent of poor recoverers developed progressive MS roughly 20 years earlier compared to good recoverers. Severe brainstem, cerebellar, or spinal cord syndrome was associated with the worst recovery. Recovery from relapses seems to be inherently determined, since the relapse-recovery amount correlated between each relapse and the following relapses, suggesting that good recoverers tended to remain good recoverers (and vice versa).

We also confirmed that poor recovery from the first relapse can precondition an individual to an earlier onset of progressive MS. Therefore, progressive disease course may be set even after one clinical event with poor recovery. The disturbing finding from our study is that no patient today would have been on a prophylactic medication before this first relapse that may set the stage for progressive MS in some individuals. Our findings imply three future strategies:

1. Consider relapse-prevention strategies as early as RIS.
2. Use early rather than late aggressive MS prevention for the critical period of early-recurrent relapses in those patients who had a fulminant relapse with poor recovery.
3. Aggressively seek recovery from any relapse.

The first two strategies may only need repurposing of existing treatment strategies with the right trial designs and early induction or aggressive medication choices in an appropriate individual.

Recent evidence shows that early active disease is important for potential treatment even at the subclinical stage. Approximately 30 percent of patients with RIS will have a clinical demyelinating event within five years of identification of their abnormal MRI, and factors independently determining this conversion to symptomatic MS are spinal cord involvement, male sex, and age under 37 years. After combining these three risk factors, the huge difference in disease behavior suggests that, in terms of relapse location, spinal cord involvement is the strongest determinant to conversion to symptomatic MS. As mentioned above, PPMS evolves directly from RIS, therefore remyelination and axonal repair strategies can interact at the stage of RIS to prevent clinical disease in the first place and to prevent progressive MS.

Measures of progressive disease—such as gray matter atrophy—seem to start as early as RIS phase. Atrophy starts predominantly in subcortical gray matter with thalamus being the driving force, which is not surprising, since thalamus is a major relay center with extensive cortical and subcortical anatomic connections. Results published as part of the RIS Consortium provide novel evidence of thalamic atrophy in RIS and are consistent with previous reports in early MS stages. Thalamic volume loss is likely due in part to disconnection caused by white matter lesions and is present early in CNS demyelinating disease. All these findings indicate a need for relapse-prevention trials in RIS.

There are two promising agents capable to induce myelin repair. Anti-LINGO-1 is a human monoclonal antibody directed against LINGO-1, protein expressed in CNS that has been shown to inhibit oligodendrocyte differentiation and myelination, survival of neurons and axonal regeneration. Anti-LINGO-1 has a potential to enhance...
CNS remyelination and neuroaxonal protection in animal models.\textsuperscript{65} Phase-II clinical trial of this product has been completed.\textsuperscript{72}

The other notable agent in this realm is human IgM22 (sHlgM22), a serendipitously identified naturally occurring antibody isolated from the sera of patients with monoclonal gammopathies lacking neurology or antibody-associated pathologies.\textsuperscript{66} Recombinant version of sHlgM22 was constructed (rHlgM22) by cloning the antibody variable region DNA sequence into an expression vector. This antibody promotes Ca\textsuperscript{2+} signaling in astrocytes, oligodendrocyte progenitor cells (OPCs) and immature oligodendrocytes (OLs).\textsuperscript{67} The proposed mechanism is that it stimulates progenitor oligodendrocytes to proliferate, as a result of antibody binding specifically to the lipid rafts on the surface of live oligodendrocytes and bringing molecules together to make a signaling complex.\textsuperscript{66,68} Most importantly, this antibody crosses the blood-CNS barrier, targets demyelinated lesions and promotes maximal remyelination within five weeks after a single low dose (25 ug/kg) in a model of MS that normally presents with little spontaneous repair.\textsuperscript{69,70}

Recombinant human IgM22 is the first antibody of IgM isotype that promotes significant remyelination in vivo and has characteristics of classic NAbs. The antibody has successfully undergone phase-I multi-center, double-blind, randomized, placebo-controlled, dose-escalation clinical trial designed to evaluate the safety, tolerability, pharmacokinetics and immunogenicity of single intravenous administrations of rHlgM22 in patients with all clinical presentations of MS.\textsuperscript{66} In 72 patients across 16 sites that were included, so far no side effects have been reported. Since rHlgM22 and anti-LINGO1 appear to act in different ways, it is possible that their combination might be particularly effective in promoting remyelination.

Another monoclonal IgM antibody (sHlgM12) has been identified as a candidate to treat MS and other diseases associated with axonal injury.\textsuperscript{71} Recombinant form rHlgM12 was generated. This antibody has no impact on the extent of remyelination in vivo or Ca\textsuperscript{2+} influx in vitro. It binds to live neurons and promotes neurite-extension (measured by brainstem N-acetyl-L-aspartate concentrations) in a virus-induced mouse model of progressive MS.\textsuperscript{71} This represents a potential treatment for MS and many neurodegenerative diseases.

Before using these promising agents in clinical trials, proper timing for their application should be established. One approach might be to initiate treatment to repair changes in progressive MS phase. However, it seems like any future remyelination-repair strategy would best be applied at the critical time of early relapse-recovery period.
if one wishes to prevent progressive MS, as well as to prevent cumulative disability burden of those poorly recovering relapses that escape the prophylactic DMD use.

**CONCLUSION**

In this article, we recapitated phases and clinical phenotypes of MS and their treatment implications, summarized the risk factors of poor prognosis in MS with emphasis on progressive disease phase, and provided an overview of the current remyelination-repair treatment concepts. The primary targets for MS treatments should encompass prevention, delay, or slowing of progressive disease onset as the key factor impacting long-term disability. Current immunomodulatory treatments in MS are insufficient to prevent long-term disability, while future agents focusing on remyelination and axonal and neuronal repair will hopefully impact the MS-related disability and proper timing of use of these agents will be crucial to limit the loss of surviving axons.

Pathological changes early in the course of MS can contribute to long-term prognosis. Already at the stage of RIS, as precursor of PPMs, there is evidence of gray matter atrophy, specifically thalamic volume loss. Incomplete recovery from early relapses, as well as poor recovery from the first relapse, can predispose to an earlier onset of progressive MS. It is also worth noting that poor recovery from any pre- and/or post-progression relapse increases cumulative disability burden. Therefore, future remyelination and axonal repair strategies will likely work the best if applied for early clinical and/or subclinical relapses to delay or ultimately prevent later progressive disease course development. Regardless the disease phase, spinal cord disease is the most important predictor of conversion between MS phases (RIS to SAMS, RIS to PPMS, SAMS/RRMS to progressive MS) and should therefore be favored for early intervention. Additionally, advanced techniques for better monitoring of in vivo remyelination-repair will be necessary to provide information about the way a particular therapy is working.

In summary, with continued advances in the treatment and understanding of MS, there are many reasons to be enthusiastic about the future of neuroprotective treatments for this condition.

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