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Title: The benefits and risks of escalation versus early highly effective treatment in patients with multiple sclerosis

Authors: Annalisa Morgan MD[1], Emma Tallantyre BMBS PhD[2,3], Daniel Ontaneda MD PhD[1,4]

Affiliations:
[1]Department of Neurology, Neurological Institute, Cleveland Clinic, Cleveland, OH, USA
[2]Division of Psychological Medicine and Clinical Neurosciences, School of Medicine, Cardiff University, Cardiff, UK
[3]Department of Neurology, University Hospital of Wales, Cardiff, UK
[4]Mellen Center for Multiple Sclerosis Treatment and Research, Neurological Institute, Cleveland Clinic, Cleveland, OH, USA

Corresponding Author:
Daniel Ontaneda MD PhD
Address: 9500 Euclid Ave, U10 Mellen Center, Cleveland, OH 44106, USA
Telf:216-218-2841
Fax: 216-445-7013
Email: ontaned@ccf.org

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Revisions:
We appreciate the comments from the reviewers and editors. We have incorporated these into the manuscript. The manuscript is improved with these edits and is now more balanced in relation to ESC and EHT approaches. We have made point-by-point responses to all the comments in a separate document and believe that we have now addressed all the points raised.

Abstract:

Introduction: Multiple sclerosis is a chronic, demyelinating, inflammatory, and neurodegenerative disease of the central nervous system that affects over 2 million people worldwide. Considerable advances have been made in the availability of disease modifying therapies for relapsing-remitting multiple sclerosis since their introduction in the 1990s. This has led to debate regarding the optimal first-line treatment approach: a strategy of escalation versus early highly effective treatment.

Areas Covered: Our review defines the strategies of escalation and early highly effective treatment, outlines the pros and cons of each, and provides an analysis of both the current literature and expected future directions of the field.

Expert Opinion: There is growing support for using early highly effective treatment as the initial therapeutic approach in relapsing-remitting multiple sclerosis. However, much of this support stems from observational real-world studies that use historic data and lack safety outcomes or randomized control trials that compare individual high versus low-moderate efficacy therapies, instead of the approaches themselves. Randomized control trials (DELIVER-MS, TREAT-MS) are needed to systemically and prospectively compare contemporary escalation versus early highly effective treatment approaches.

Keywords: Disease modifying therapies; DMTs; Early highly effective treatment; EHT; escalation approach; ESC; relapsing-remitting multiple sclerosis; RRMS

Article Highlights:

1. The two most common treatment approaches in relapsing-remitting multiple sclerosis are a strategy of escalation (ESC) and early highly effective treatment (EHT).
2. EHT is associated with improved disability outcomes in observational data but may have higher risks.
3. ESC may lead to effective treatment but risks therapeutic inertia and disability accrual.
4. There is growing support for using EHT, but most of the current evidence, which stems from observational, comparative data, has limitations in the applicability of their results to contemporary patients.
5. Prospective randomized control trials (DELIVER-MS, TREAT-MS) are needed to better compare and evaluate these approaches using current practice guidelines.

Body of the article:

Introduction

Multiple sclerosis (MS) affects an estimated 2.8 million people worldwide and approximately 1 million in the USA alone.[1] MS is a chronic, demyelinating, inflammatory, and neurodegenerative disease of the central nervous system.[2-3] MS is more common in women and initially follows either a relapsing-remitting (RR) or primary progressive (PP) course.[2-3] Disease modifying therapies (DMTs) were first introduced in the 1990s with interferon beta-1b as the first treatment for MS.[3] Since that time, there have been considerable advances in the number, efficacy, and safety of therapeutics for MS, principally for RRMS.[2-7] There are now over two dozen US Food and Drug Administration (FDA)-approved therapies with more under development.[2-7] However, the increase in available DMTs has also led to increased debate in the MS field regarding the optimal first-line treatment approach in this patient population.[2-14] This debate partly arose from

a need to make accessible treatment frameworks out of the abundant treatment options, and 2 main approaches have now arisen.[2-14] These approaches include a strategy of escalation (ESC) versus a strategy of early highly effective treatment (EHT).[2-14]

Both the ESC and EHT approaches prioritize early treatment in a patient's disease course. This is based on prior studies demonstrating improvement in relapses and other disability outcomes with earlier treatment in people with RRMS.[2,4-6] The approaches differ in which DMT medication classes they consider as first-line therapeutic options.[2-14] DMTs can be divided into low-moderate versus high efficacy therapies.[2-7] However, it is also important to acknowledge that this dichotomy is somewhat arbitrary given variations in efficacy across Phase 3 studies that utilize different outcomes measures (Table 1).[3-4] For example, fingolimod has been classified as both a moderate and high efficacy therapy in different studies, and its classification can also reflect varied standard of care practices between countries as well.[9-14] Typically, low-moderate efficacy therapies include interferons, glatiramer acetate, teriflunomide, dimethyl fumarate, and the sphingosine 1-phosphate receptor (S1P) modulators as their annualized relapse rate (ARR) reduction versus placebo ranges from 28-55% (Table 1).[3-4] High efficacy therapies include anti-CD20 agents, natalizumab, cladribine, and alemtuzumab as they reduce the ARR by 46-68% versus either placebo or an active comparator (Table 1).[3-4] There are similar differences in brain volume loss effects between low-moderate and high efficacy therapies as well (Table 1).[3-4] The high efficacy therapies can also be further subdivided into either induction therapies, which includes therapies that are administered intermittently but have long lasting effects on the immune system, versus maintenance therapies, where medications are administered continuously.[2,5,8] The use of induction therapies replicates the treatment regimens of other

autoimmune conditions, including rheumatologic diseases, where it is a widely used technique.[2] The use of autologous hematopoietic stem cell transplantation (AHSCT) as a high efficacy DMT is outside the scope of this article but has been reviewed in detail elsewhere.[15]

The higher efficacy treatments may be associated with increased adverse side effects (Figure 1).[2-8] This includes higher infection, autoimmune, and malignancy risks.[2-8] These risks may be evident in Phase 3 trials, but risks that are rare, and/or related to treatment duration usually only become evident in longer-term studies.[2-4,7] This makes it difficult to truly quantify risk with Phase 3 studies alone as they often only systematically evaluate the first two years of a medication's risk.[2-4,7] Additionally, a patient's willingness to accept different levels of risk can vary based on multiple factors.[16]

Ultimately, the ESC and EHT approaches counter-balance the benefits of early, efficacious treatment with potential adverse effects.[2-14] Our review provides an overview of these approaches, highlights the pros and cons of each approach and the evidence that supports them, and outlines our assessment regarding these approaches and the important future directions of the field to further optimize treatment regimens in people with MS.

1. Definitions of the ESC and EHT Approaches

Often seen as the traditional approach, the ESC approach is more risk-averse as it uses first-line low-moderate efficacy medications with more favorable risk profiles (Figure 2).[2-14] If the patient's disease remains inactive on these low-moderate efficacy therapies, then they will

remain on these safer medications.[4] However, if there is continued disease activity, then they can be offered escalation to higher efficacy medications.[4]

In comparison, the EHT approach is a more contemporary approach that utilizes a "higher risk, higher reward" strategy.[2-14] It focuses on maximizing anti-inflammatory effects earlier in the disease course by using first-line high efficacy therapies (Figure 2).[2-14] This approach is especially preferred for people with RRMS who have prognostic factors associated with more severe disease.[2,4-5,8] Providers mitigate some of the higher risks associated with these therapies using screening tests (e.g. JCV serology) and preventative medications (e.g. vaccinations prior to DMT initiation).[2-5,8] However, despite this becoming an increasingly more popular approach in recent years, it has not become the sole, preferred treatment approach, and the ESC approach is still widely used.[2-14] The increased safety risk, in combination with other factors including convenience and expense, continue to play a role in limiting the widespread use of this approach.[2-14]

2. Pros and Cons of ESC Approach

The ESC approach appears attractive as many patients can be effectively treated using low-moderate efficacy medications with safer risk profiles. Evidence suggests that 23-37% of people with MS will demonstrate no evidence of disease activity (NEDA) after 2 years of low-moderate efficacy DMTs (Table 1).[4] Appropriate patient selection for this approach may include identifying patients with a lower risk of severe disease activity.[4,17-18] Clinical predictors of less severe disease at baseline include less frequent relapses, female sex, younger age at onset, relapses that involve sensory instead of motor or brainstem symptoms, and complete recovery

after relapses.[4,17] MRI characteristics predictive of less severe disease include lower T2 lesion burden, lower number of gadolinium enhancing lesions, absence of visible brain atrophy, absence of persistent T1 hypointense lesions, and absence of infratentorial or spinal cord lesions.[4,17-18]

Low-moderate efficacy therapies consist of older injectable agents and oral medications.[3-4,19] Older injectable medications (interferons, glatiramer acetate) typically reduce the ARR by 29-34% and oral medications by 36-58% (Table 1).[3-4] Studies have also demonstrated the effectiveness of some low-moderate efficacy DMTs at reducing secondary outcomes such as brain volume loss and disability progression (Table 1).[4,20-21] The efficacy of early use of these medications extends to limiting the conversion of clinically isolated syndrome (CIS) to clinically definite MS.[22]

The low-moderate efficacy medications are often associated with only mild to moderate risk.[3-4] The most common side-effects of the older injectables are flu-like symptoms, injection site reactions, and liver enzyme elevations.[3-4] Serious adverse events are rare in low-moderate efficacy DMTs but include infection, rarely including progressive multifocal leukoencephalopathy (PML), bradycardia, atrioventricular block, and gastritis.[3-4] The more favorable risk profile of these medications is important as studies have shown that often people with MS are risk averse.[16] A study conducted by Fox et al. showed that 75% of their study population had a lower risk tolerance level than that associated with the risk of PML in the use of the high efficacy treatment, nataliuzamab.[16] Additionally, patients with more information-seeking behavior were less risk tolerant.[16] This is important to know as the 2017 revisions to the

McDonald diagnostic criteria for MS allow for earlier diagnosis.[4] This means that providers may now be asking a more risk averse population to make earlier treatment decisions, possibly pushing them towards the low-moderate efficacy medications in the ESC approach as they may feel that they do not have time to gather needed information to select the riskier EHT approach. In a disease that more commonly affects women, the safety profile of medications and risk tolerance of the population are also important to consider as they relate to decisions regarding family planning.[23] As the low-moderate efficacy medications have been available for longer, there is more data surrounding their safety in pregnancy. Glatiramer acetate can even be continued throughout pregnancy and interferon betas and fumarates until the time of conception.[23]

Despite the many attributes of the ESC approach, there are also several shortcomings. One shortcoming is the lack of an established, universal definition of what constitutes continued disease activity and criteria for monitoring or escalating therapy.[2-14,24-25] For example, historically providers had a higher threshold for escalation, such as only considering escalation in the setting of a clinical relapse, and surveillance magnetic resonance imaging (MRI) monitoring was not routinely employed.[9,12] Now, surveillance MRI is recommended for all people with MS on DMTs, and subclinical evidence of disease activity on MRI may prompt earlier escalation in therapy.[26] This makes it challenging to interpret the findings of real-world studies using historic data, which may include people with MS managed with outdated ESC approaches.[9-14]

The Rio and modified Rio scoring systems were derived from noting that patients treated with interferon beta-1a with relapses, disability progression, and new T2/gadolinium enhancing

lesions on MRI were found to have a higher risk of future relapses and disability progression.[2,4,24-25] However, the Rio and modified Rio systems have not been extensively studied for other DMTs and since then more stringent targets for subclinical disease activity have been suggested, making it challenging to create consistent guidelines and scoring systems to assist with the escalation approach.[2,4,24-25] Outcomes, such as no evidence of disease activity (NEDA), which includes the absence of relapses, new lesions on MRI, and disability progression in NEDA 3 (NEDA 4 also incorporates brain atrophy) are being used with increasing frequency.[2,4,27-31] Ongoing ways to incorporate outcomes such as cognition and biomarkers, like neurofilament, are also under discussion.[4,28] The push to incorporate broader outcome measures stems from recent studies that have shown evidence that progression independent of relapse (PIRA) appears to play the largest role in disability accumulation in RRMS.[32-33] The caveat is that while many of these newer measures have shown promise in predicting group outcomes, their effect at an individual level is uncertain.[2,4,27] The low likelihood of achieving some of these newer outcomes, such as NEDA, even using high efficacy DMTs, raises questions about their utility as well.[2,4,28-31] Additionally, the cost and discrepancies between various MRI software packages needed for the measurement of certain outcomes (e.g. brain atrophy) makes them inaccessible to all providers, and therefore, impossible to use for consistent escalation decisions at this time.[2,27-28] Overall, these factors highlight the continued concern that providers are not well equipped to escalate therapies in a timely manner, which leads to missed opportunities in administering effective therapies early in the disease process and higher rates of disability accrual and associated cost.[2-14,34]

Another limitation of this approach is the possibility of therapeutic inertia, defined as the accepted lack of treatment initiation or escalation in the setting of continued disease activity.[35] Multiple physician, patient, and healthcare factors contribute to this concept, including a physician's low tolerance of uncertainty, a patient's misinterpretation of continued disease activity or aversion to new DMT side effects, and the healthcare system's lack of guidelines and high costs associated with some therapies.[35]

Even if therapeutic inertia does not occur and therapy escalation is decided in a timely manner, the process of escalating can suffer delays depending on the initial therapy.[2,5] For instance, washout periods may be needed, which adds time off medication and may introduce more risk to the patient given the risk of rebound disease activity with stopping S1P modulators.[2,5,36] Washout periods also do not eliminate the additive risks of medications as patients are escalated, as evidenced by the increased risk of PML with natalizumab in the setting of prior immunosuppressive therapy use.[5,37]

The mode of administration of low-moderate efficacy medications can lead to non-adherence as well.[38] Adherence rates for injectable and oral medications have ranged from 41-88% in studies, with non-adherence for injectables mainly attributable to difficulties with injections and injection-site reactions.[38] Additionally, studies noted that 20% of patients taking oral medications were non-adherent to once or twice daily dosing and 25% of patients discontinued their therapy within one year.[38]

3. Pros and Cons of EHT Approach

Early highly effective therapy (EHT) takes a more proactive approach, using high-efficacy therapies as first-line agents to maximize their anti-inflammatory effects.[2-14] This is especially important in people with MS who have more active disease states and associated higher risk of disability accural.[4,12,17-18] This has been noted in a study by Harding et al. where patients who received EHT had higher ARRs at baseline than their comparison group who underwent ESC, but the EHT group still had improved disability outcomes as measured by a lower 5-year change in extended disability status scale (EDSS).[12] Studies have shown that people with MS with greater levels of disability are also willing to accept higher levels of DMT related risks.[16] The high efficacy of these medications is a clear advantage of this approach.[2-14,39-44] High efficacy therapies are so-called because of greater reductions in ARR versus placebo or active comparators (Table 1).[3-4] Additionally, they are associated with reductions in the rates of disability progression, new T2/gadolinium enhancing lesions on MRI, conversion from CIS to clinically definite disease, and conversion of RRMS to secondary progressive MS (SPMS).[2-8,39-45] There is growing data that these medications are also effective at reducing contemporary markers of disease progression, such as PIRA and brain atrophy (Table 1).[4,32-33] High efficacy medications have shown a brain volume percent loss per year of -0.24 to -0.36 in comparison to low-moderate efficacy medications that range from -0.37 to -0.60 per year (Table 1).[4] Additionally, 37-47.7% of people with MS will demonstrate NEDA after 2 years of high efficacy DMTs compared to 14.2-37% with low-moderate efficacy DMTs (Table 1).[4] However, it is not just the high efficacy therapies themselves, but the fact that these medications are being administered early in a patient's disease course that makes the EHT approach efficacious.[11-12] This is demonstrated by studies showing that patients who received high efficacy treatment

within two years of disease onset had lower levels of disability when compared with those who were initiated later in their disease course.[11]

While EHT leads to reduced rates of disease and disability progression when compared to low-moderate efficacy medications as outlined above, it does not reduce this rate to zero.[2-14,39-44] This is important to consider as this patient population typically requires long-term treatment with immunosuppression and when caring for the individual patient as opposed to a group, since this may change the perceived benefits and risks of starting EHT. When compared to low-moderate DMTs, high efficacy therapies are often associated with higher risks of infection, which can include life threatening events, autoimmunity, and malignancy.[2-8,46-53] Natalizumab is associated with higher risks of PML in patients with JC virus seropositivity, and this risk is increased with prolonged use of the medication.[46] Anti-CD20 agents have been associated with higher rates of serious infections, those that required hospitalization, when compared to other DMTs as well.[47] The coronavirus disease 2019 (COVID-19) pandemic significantly influenced how the MS field perceives infection risk and highlighted that anti-CD20 DMTs increase the risk of severe COVID and attenuate humoral vaccine responses.[48-51] Reassuringly, people with MS were not shown to have high degrees of mortality associated with COVID-19.[48] However, rituximab and ocrelizumab use were associated with more severe infections, including the need for hospitalization and/or ICU admission, if a patient had COVID-19.[49-50]

Alemtuzumab is associated with the development of novel autoimmune conditions, including a risk of thyroid disease, immune thrombocytopenia, antiglomerular basement membrane disease, and hepatitis.[3-4] All DMTs, even low-moderate efficacy therapies, are associated with a

theoretical elevated malignancy risk in comparison to the general population given their effect on immunosurveillance, which is an integral component of the body's defense against malignancy.[52-53] Less long-term data is available regarding the malignancy risk associated with newer high efficacy therapies. Some studies have reported alemtuzumab and ocrelizumab to have an increased risk of malignancy compared to interferon/placebo.[3,44] However, a caveat to this is that while ocrelizumab was associated with a higher risk of breast cancer when compared to a pooled group of patients who received interferon beta-1a or placebo, this was still a lower risk than the general population, and recent long term registries have not shown this increased risk compared to the general population.[44,54] It is also important to note that if medications need to be stopped due to the occurrence of malignancy or other adverse effects, there is still a risk of ongoing or rebound disease activity, particularly with natiluzimab.[5,55]

Additionally, the costs associated with the high efficacy therapies, including administering the therapies and monitoring for adverse effects, can be high.[2-4,56-59] Studies have shown that oral therapies have the lowest associated all-cause and MS-related claims-based costs.[57] The annual costs associated with high efficacy infusion therapies could equate to over $100,000, which could still be an underestimation as it is unclear if all monitoring data was included.[58] However, for therapies like alemtuzumab that use an induction technique, these analyses may be falsely inflated since they do not summate the costs beyond 2 years when patients no longer receive infusions and costs are limited to post-treatment monitoring.[58-59] Continued advances, such as the availability of a subcutaneous anti-CD20 DMT, ofatumumab, may also result in more favorable cost profile options for high efficacy DMTs moving forward.[60]

4. Observational, Comparative Data Between Approaches

Most of the data that supports decision making between these approaches comes from observational, comparative studies (Table 2).[9-14]

Buron et al. showed that initial EHT led to a lower probability of a first on-treatment relapse and 6-month confirmed EDSS score worsening.[9] 75 patients (38.7%) were escalated to high efficacy therapy after a mean of 3.1 years, in the setting of non-specified evidence of breakthrough disease activity.[9] Subgroup analyses included: reclassifying fingolimod as a low-moderate efficacy therapy and only including patients with high baseline disease activity, which were comparable to the results of the main analyses.[9]

Brown et al. demonstrated that initial treatment with EHT was associated with a lower conversion from RRMS to SPMS when compared to initial treatment with low-moderate efficacy therapies.[10] This study also demonstrated that even when the low-moderate efficacy therapies were escalated to high efficacy therapies, either within 5 years or after 5 years (a mean time to escalation was not reported), the risk of progression to SPMS remained higher.[10]

He et al. demonstrated that early high efficacy therapy, within 2 years of disease onset, was associated with less disability (as measured by the difference in EDSS during follow-up at 6-10 years after disease onset) than late high efficacy therapy, started 4-6 years from disease onset.[11] Patients could still be included in the analysis if they had been treated with low-moderate efficacy medications (including interferons and oral medications) before high efficacy therapies as well, which is different from the definition of EHT we refer to in this article.[11] A secondary

analysis showed a lower hazard of disability progression from disease onset in the early treatment group.[11] This outcome also persisted after year 6 by which time all participants had received at least one high efficacy therapy.[11]

Harding et al. demonstrated a lower 5-year change in EDSS with initial EHT.[12] The secondary outcome of sustained accumulation of disability (SAD) occurred in a median of 6 years with EHT and 3.1 years with ESC.[12] Those in the ESC group were regularly clinically +/- radiographically monitored according to standard clinical care at the time to determine if escalation of therapy was needed.[12] Only 58 patients (11.9%) were escalated, almost always in the setting of clinical relapse, with a median escalation time of 2.4 years to high efficacy treatments.[12] Even the patients who escalated therapies in the ESC group showed a median time of 3.3 years to SAD with 60% of the group having already achieved SAD before escalation.[12] However, the results evaluating SAD between approaches were not statistically significant.[12] The median baseline EDSS was comparable between groups, but the EHT group had a higher baseline ARR.[12] If anything this makes the results even more compelling since the EHT group had more adverse prognostic indicators at baseline, and yet did better in terms of EDSS change.[12] However, the low rates of escalation, long interval until escalation, and predominant use of clinical triggers to determine the need for escalation to high-efficacy therapy reflect an outdated ESC approach, and this data should be applied to contemporary cohorts with caution.[12]

Spelman et al. showed less disability progression in a Swedish cohort where EHT was a more common initial approach (34.5%), compared with a Danish cohort where EHT was significantly lower (7.6%).[13] In the Danish cohort, 92.4% of patients were initiated on low-moderate efficacy

therapies versus 65.5% of the Swedish cohort.[13] The Swedish cohort had a 29% lower rate of disability progression in comparison to the Danish cohort.[13] However, the statistical significance of these results was lost with propensity score-weighted modeling.[13] 554 patients (27.8%) escalated (unspecified reasons for escalation) to high efficacy therapies in the Danish cohort and 585 patients (34.7%) escalated to high efficacy therapies in the Swedish cohort.[13]Although this was not an actual comparison of the approaches, it was a comparison of 2 cohorts that were strongly enriched for either the EHT or ESC approach, reflecting different treatment approaches between countries.[13] The study did note that the Danish cohort had significantly higher rates of discontinuing the initial DMT and switching to alternative DMTs when compared to the Swedish cohort.[13] The Danish cohort was more likely to discontinue initial therapy due to a lack of effectiveness (37.4% versus 30.7%, respectively); whereas, the Swedish cohort was slightly more likely to discontinue initial therapy due to adverse effects (34.5% versus 33.8%, respectively).[13] However, no statistical analysis was completed to determine if the differences in discontinuation due to lack of efficacy or adverse effects were significant between groups.[13]

Iaffaldano et al. demonstrated that initial EHT had lower rates of disability progression compared to an ESC approach.[14] The EHT group had an overall significantly lower mean delta-EDSS compared to the ESC group throughout the follow-up period, and the mean delta-EDSS differences between the 2 groups were 0.1 at 1 year, 0.3 at 5 years, 0.64 at 8 years, and 0.67 at 10 years.[14] Treatments were escalated for “lack of efficacy” in the setting of clinical relapse and/or increased T2/gadolinium enhancing lesions on MRI, but median time to escalation was 6.3 years, which seems surprisingly long when compared to contemporary standards of escalation.[14]

While these observational, comparative studies have provided a good starting point for discussion about an ESC versus EHT approach, the discrepancies in escalation parameters and outdated approaches to escalation utilized in some studies makes it difficult to apply these results with confidence to contemporary patients.[9-14] The interpretation of these results may also be flawed based on varied definitions of an ESC versus EHT approach.[11] For instance, 267 patients in a study by He et al. underwent initial therapy with low-moderate efficacy DMTs before being escalated to high efficacy therapies.[11] However, they were still included in the analysis of the early high efficacy therapy group despite this being more reflective of a contemporary ESC rather than an EHT approach.[11] Additionally, despite several of these studies utilizing propensity scoring to match baseline characteristics between groups, continued bias in the selection of patients receiving initial high versus low-moderate efficacy therapies may still be influencing the results.[9-11,13-14] Lastly, these studies lack or have extremely limited reports of safety outcomes.[9-14] This is perhaps the most pertinent critique of these studies since a higher risk of adverse effects is often cited as the main limitation in the utilization of the EHT approach.[2-8,46-55]

5. Randomized Control Trials (RCTs) Comparing Approaches

To date, there are no available head-to-head RCTs comparing ESC and EHT approaches. There are only RCTs that compare individual high efficacy therapies to low-moderate efficacy therapies.[32,40-42,44] These studies have shown increased efficacy in terms of improved freedom from clinical disease activity and sustained reduction in disability with high efficacy therapies.[32,40-42,44] However, this data is of limited utility in the discussion of EHT versus ESC approaches since the trials are double-blinded and have limited long-term follow-up. [32,40-42,44] This means that participants randomized to the lower-efficacy DMT were not monitored nor

expected to change from their allocated therapy group even if they experienced continued disease activity, which is a significant deviation from our current definition of an ESC approach.[32,40-42,44]

Two large, RCTs, DELIVER-MS (Determining the Effectiveness of earLy Intensive Versus Escalation Approaches for the treatment of Relapsing-remitting MS, NCT03535298) and TREAT-MS (TRaditional versus Early Aggressive Therapy for MS, NCT03500328), aim to bridge this knowledge gap (Table 3).[61-63] DELIVER-MS and TREAT-MS are now actively enrolling patients and will compare these 2 approaches using contemporary disease outcomes and escalation parameters.[61-63] The primary outcome in DELIVER-MS will be whole brain volume loss change from baseline to 36 months and secondary/tertiary outcomes will include a variety of clinical assessments, MRI metrics, and patient reported outcomes (including a patient's satisfaction with their chosen DMT and treatment outcomes).[61] Patients are allowed to escalate therapy in the ESC group based on clinical and/or MRI activity, side effects, or convenience after receiving an initial dose of the low-moderate efficacy medication.[61] Outcomes in TREAT-MS will consist of clinical assessments (with the primary outcome being time to sustained disability progression using EDSS plus), cognitive and ophthalmologic testing, MRI results, and patient reported outcomes from baseline to 63 months.[62-63] If breakthrough disease, unspecified definition, is noted during this study, then patients are randomized to either escalate to a high efficacy therapy or another low-moderate efficacy therapy with a different mechanism of action.[62-63]

Conclusion

Advances in the availability, efficacy, and varied safety profile of DMTs for RRMS since their introduction in the 1990s has led to debate regarding the optimal first-line treatment approach.[2-14] Two approaches have arisen from this debate: a strategy of escalation (ESC) versus a strategy of early highly effective treatment (EHT).[2-14] However, there is a lack of RCTs directly comparing these approaches and the majority of evidence is provided by observational, comparative data or RCTs that compare low-moderate versus high efficacy therapies instead of the actual treatment approaches.[9-14, 32,40-42,44] DELIVER-MS and TREAT-MS are the first large, blinded RCTs to directly compare these approaches using current treatment and escalation guidelines.[61-63] These trials will also report on risks associated with contemporary ESC versus EHT approaches. Continued observational, surveillance data will still be needed after the conclusion of these studies to better assess longer-term outcomes and extensions of both studies are planned. They are currently enrolling patients and will provide the MS field with needed data to better support our clinical decision making in the treatment of people with RRMS.

Expert Opinion:

There is growing support for using EHT as the initial treatment approach in people with relapsing MS based on the current literature.[9-14,32,40-42,44] However, much of this support stems from observational studies that use older approaches to escalation and monitoring and lack safety outcomes.[9-14] This support also stems from RCTs that compare individual high versus low-moderate efficacy therapies, instead of the approaches themselves.[32,40-42,44] While these studies demonstrated improved efficacy of the high efficacy therapies, they are limited in their applicability to EHT versus ESC approaches as patients were not allowed to change from their initial therapy even if they experienced continued disease activity. [32,40-42,44] Additionally, not all

of these studies reported safety outcomes, which are a key consideration when deciding between DMTs and approaches.[32] RCTs that directly compare contemporary ESC and EHT approaches and evaluate both clinical and radiographic markers of continued disease activity as well as safety outcomes are needed to further optimize the care of people with MS.[61-63]

DELIVER-MS and TREAT-MS are large RCTs currently enrolling participants that utilize contemporary practice guidelines in an effort to bridge our knowledge gap, and the results will enhance our ability to counsel people with MS regarding their available treatment options.[61-63] We anticipate that these studies will also lead to additional avenues of research, including expanding outcome measures to assess the likelihood of continued disability progression independent of inflammatory activity and the long-term risks of the different approaches. We also expect that this expansion will include further evaluation of the role that therapies may play in remyelination and consideration of how this outcome may differ between treatment approaches. AttackMS (Natalizumab for the Treatment of People With Inflammatory Demyelination Suggestive of Multiple Sclerosis, or Definite Multiple Sclerosis, at First Presentation, NCT05418010) is a current trial evaluating this outcome by assessing the influence of initial highly effective therapy, specifically natalizumab, on remyelination. Additionally, it will be interesting to see how AHSCT is incorporated into treatment approaches as new data is made available from studies such as BEAT-MS (Best Available Therapy Versus Autologous Hematopoietic Stem Cell Transplantation for MS, NCT04047628) and StarMS (Autologous Stem Cell Transplantation versus Alemtuzumab, Ocrelizumab, Ofatumumab, or Cladribine in RRMS, ISRCTN88667898).[15,64] One may even envision the potential for using AHSCT in trials of treatment naïve patients with further improvements in the safety of this therapy.[15,64]

Regarding how the field will evolve in 5 years, we predict that new evidence will continue to support EHT as the initial treatment approach in people with RRMS. However, we recognize that even with more supportive data for EHT, some people with MS will still choose the ESC approach for various reasons. This means that future research efforts will still need to focus on improved optimization of the ESC strategy, including a more standardized approach to escalation as this has remained extremely variable between studies.[9-14,32,40-42,44] We also anticipate that as EHT is used with increased frequency and more data is available regarding the long-term adverse effects of these medications, a large, future research focus will encompass determining the optimal timing of de-escalation of therapies. On the opposite end of the spectrum, an increased use of EHT may lead to consideration of how this approach can be used even earlier in a patient's disease course as well. Early use of DMTs at even the point of radiographically isolated syndrome (RIS) has been associated with reduced conversion to clinically definite disease, but it remains unclear if the utilization of the EHT approach at this time point would balance improved long-term outcomes with acceptable safety outcomes.[65] Trials are currently underway to better address this question.[66]

Overall, large trials examining treatment approaches in MS will considerably influence our current practice and play a large role in shaping the future of DMT treatment in the MS field. [61-64,66]

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Figures:

Figure 1: Relationship Between Efficacy and Adverse Side Effects of DMTs

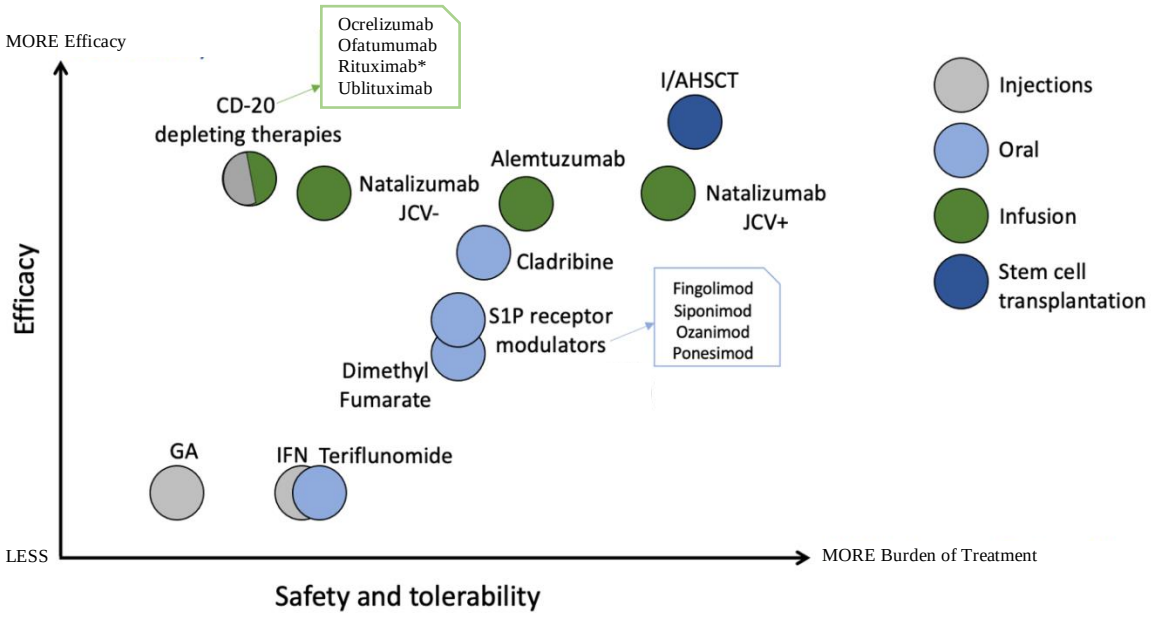


Figure revised from Hughes et al. (67)

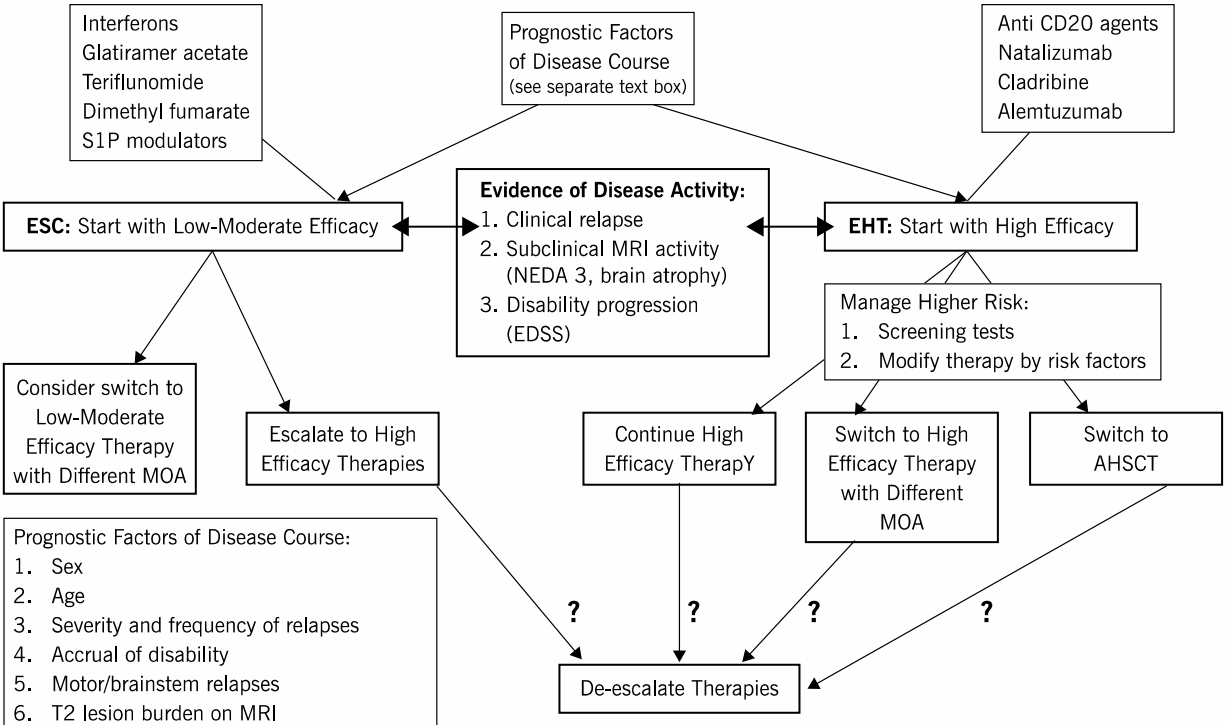
*Off-label treatment

Efficacy as presented on the y axis relates to the effect of disease modifying therapies on annualized relapse rate.

AHSCT: autologous stem cell transplantation, DMTs: disease modifying therapies, GA: glatiramer acetate, I: immunoablation, IFN: interferons, JCV: JC virus, S1P: sphingosine 1-phosphate receptor

Figure 2:

Figure 2: Escalation (ESC) versus Early Highly Effective Treatment (EHT) Approaches[3-4,17-18]



AHSCT: autologous stem cell transplantation, EDSS: expanded disability status scale, EHT: early highly effective treatment, ESC: escalation, MOA: mechanism of action, MRI: magnetic resonance imaging, NEDA 3: no evidence of disease activity 3, S1P: sphingosine 1-phosphate receptor

Tables:

Table 1:

Table 1: Outcomes Across Studies and Disease Modifying Therapies (DMTs)				
DMT	Route	Outcome Measures		
		ARR Reduction vs Placebo	Rates of NEDA 3	Brain Atrophy (% brain volume loss/year)
Interferon betas:				
Interferon Beta-1a	IM/SC	32%[68] 32%[71]	14.2% at 96 weeks[69] 27.1% at 96 weeks[44]	-0.53[70] -0.45 to -0.55[40-41,44,71]
Interferon Beta-1b	SC	34%[72]		
Pegylated Interferon Beta-1a	SC	28%[73]	37% at 2 years[74]	
Glatiramer acetate	SC	29%[75]		-0.44[76]
S1P receptor modulators:	Oral			
Fingolimod		54%[20] 52%[21]	31% at 2 years[77]	-0.37 to -0.48[20,78]
Siponimod		55%[79]		
Ozanimod		48% (compared to interferon beta-1a)[80] 38% (compared to interferon beta-1a)[81]		
Ponesimod		30.5% (compared to teriflunomide) [82]		
Fumarates:	Oral			
Dimethyl fumarate		44-53%[83-84]	26% at 2 years[85]	-0.39 to -0.60[83-84]
Monomethyl fumarate		44-48%[83-84]		
Diroximel fumarate		44-48%[83-84]		
Teriflunomide	Oral	31%[86]	23% at 108 weeks[87]	-0.51[86]
Cladribine	Oral	58%[88]	46% at 2 years[89]	
Natalizumab	IV	68%[90]	37% at 2 years[91]	-0.24[92]
Anti-CD20 monoclonal antibodies:				
Ocrelizumab	IV	46-47% (compared to interferon beta-1a)[44]	47.7% at 96 weeks[93]	-0.34 to -0.36[44]
Ofatumumab	SC	51-59% (compared to teriflunomide)[94]		
Ublituximab	SC	49-59% (compared to teriflunomide)[95]		
Alemtuzumab	IV	55% (compared to interferon beta-1a)[40] 49% (compared to interferon beta-1a)[41]	39% at 2 years[40]	-0.22 to -0.25[40-41]

ARR: annualized relapse rate, DMT: disease modifying therapy, EDSS: expanded disability status scale, IM: intramuscular, IV: intravenous, NEDA 3: no evidence of disease activity 3, S1P: sphingosine 1-phosphate receptor, SC: subcutaneous, vs: versus

Table 2:

Table 2: Observational, Comparative Data Between Approaches					
Study	Sample Size	DMTs	Methodology	Outcomes	Limitations
Brown et al.[10]	1555	Fingolimod Natalizumab Alemtuzumab GA Interferons	1. Initial EHT: fingolimod, natalizumab and alemtuzumab 2. Initial therapies in ESC: GA, interferons 3. SPMS: total EDSS increased by 1 point (baseline ≤5.5) or by 0.5 points (baseline >5.5) that occurred in absence of relapse, confirmed on repeat testing within 3 months, and resultant EDSS ≥4 4. Baseline characteristics matched between groups 5. Minimum 4-year follow-up	1. Initial EHT with lower conversion to SPMS (HR: 0.66, absolute 5-year risk of progression: 7% in EHT vs. 12% ESC) 2. When initial ESC therapies escalated to high efficacy therapies ≤5 years or >5 years risk remained higher (HR: 0.76, absolute 5-year risk of progression: 8% vs. 14%)	1. Lack of rationalization for DMT escalation 2. Use of only total EDSS 3. Lack of reported safety outcomes
Harding et al.[12]	592	Natalizumab Alemtuzumab Interferons GA DF Fingolimod Teriflunomide	1. Initial EHT: natalizumab, alemtuzumab 2. Initial therapies in ESC: interferons, GA, DF, fingolimod, teriflunomide 3. Change in EDSS and SAD: increase in EDSS of 1.5 (baseline 0) or 1 (baseline 1-5.5) or 0.5 (baseline ≥5.5) sustained for 6 months 4. Median baseline EDSS comparable in 2 groups 5. EHT group had higher baseline ARR compared to ESC 6. Patients escalated to high efficacy therapy in the ESC group had higher baseline ARRs than their non-escalated counterparts 7. Follow-up at 5 years	1. Lower 5-year EDSS change with EHT (adjusted ß:-0.85) 2. Median 6 years to SAD with EHT vs. 3.1 with ESC 3. 58 patients (11.9%) were escalated with median escalation time of 2.4 years 4. Median 3.3 years to SAD in patients who escalated therapies with ESC group (60% had already achieved SAD before escalation)	1. Outcomes evaluating SAD were not statistically significant 2. No propensity scoring was used 3. Low rates, long interval, and predominant use of clinical triggers for escalation reflect an outdated ESC approach 4. Limited safety data was reported
Buron et al.[9]	388	Natalizumab Fingolimod Alemtuzumab Cladribine Daclizumab Ocrelizumab Interferons	1. Initial EHT: natalizumab, fingolimod, alemtuzumab, cladribine, daclizumab, ocrelizumab	1. EHT with lower probability of first on-treatment relapse (HR: 0.50, 50% lower rate) and 6-month confirmed EDSS score worsening	1. Incomplete MRI parameters 2. Limited rationalization for DMT escalation and no secondary analysis performed on

		Teriflunomide DF GA	2. Initial therapies in ESC: interferons, teriflunomide, DF, GA 3. First on-treatment relapse and 6-month confirmed EDSS worsening: increase of $\geq$1.5 (baseline 0) or $\geq$ 1 (baseline 1+) 4. Propensity score matching used since EHT more likely with younger age, male sex, increasing baseline relapse rate and/or EDSS, and shorter baseline disease duration 5. Follow-up at 4 years	(HR: 0.53, 47% lower rate) 2. 75 patients (38.7%) were escalated to high efficacy therapies after a mean of 3.1 years 3. Subgroup analyses: reclassified fingolimod as a low-moderate efficacy therapy (HR: 0.47, 53% lower rate of 6-month confirmed EDSS score worsening with EHT) and only included patients with high baseline disease activity (HR: 0.48, 52% lower rate of 6-month confirmed EDSS score worsening with EHT and HR: 0.60, 40% lower probability of first relapse with EHT)	outcomes after patients were escalated 3. Lack of reported safety outcomes
He et al.[11]	544	Rituximab Ocrelizumab Mitoxantrone Alemtuzumab Natalizumab	1. EHT (NOT necessarily the initial therapy): rituximab, ocrelizumab, mitoxantrone, alemtuzumab, natalizumab 2. Early EHT: 0-2 years after disease onset 3. Late EHT: 4-6 years after disease onset 4. Difference in EDSS and disability progression: increase in EDSS of 1.5 (baseline 0), 1 (baseline >0 but $\leq$5.5), or 0.5 points (baseline >5.5) for at least 6 months 5. Baseline characteristics matched between groups 6. Overall cohort young with active disease early in the disease course 7. Outcomes measured at 6-10 years after disease onset (median follow-up of 7.8 years)	1. Early EHT associated with lower EDSS at 6-10 years (-0.98 point mean difference in EDSS between groups, minimal change throughout follow-up, ß: -0.06) 2. Lower hazard of disability progression from disease onset in early treatment group (HR: 0.46). Outcome continued after year 6 when both groups were on high efficacy therapies (HR: 0.38)	1. Patients in either group may have undergone an ESC approach instead of a contemporary EHT approach 2. Lack of reported safety outcomes
Spelman et al.[13]	4861	Fingolimod Natalizumab Rituximab Alemtuzumab Ocrelizumab Interferons	1. Initial EHT: fingolimod, natalizumab, rituximab, alemtuzumab, or ocrelizumab	1. EHT was associated with lower levels of disability progression at 24 weeks 2. Swedish cohort (EHT) had 29% lower rate of	1. Limited rationalization for DMT escalation 2. Statistical significance of results was lost with

		GA DF Teriflunomide	2. Initial therapies in ESC: interferons, GA, DF, teriflunomide 3. Disability progression: increase in EDSS of at least 1 point from baseline (1.5 if baseline 0 and 0.5 if baseline ≥5.5) sustained for at least 6 months 4. Analyses divided by Danish and Swedish registries: significant differences in sex and relapse rates at 12 and 24 months prior to baseline between registries 5. Outcomes measured at 24 weeks	disability progression (HR: 0.71) in comparison to the Danish cohort (ESC). But the statistical significance of these results was lost with propensity score-weighted modeling (HR: 0.97) 3. 27.8% escalated to high efficacy therapies in Danish cohort and 34.7% escalated in Swedish cohort	propensity score-weighted modeling 3. Compared 2 cohorts that modeled the approaches, but were not an actual comparison of the approaches themselves 4. Limited safety outcomes were reported
Iaffaldano et al.[14]	2702	Fingolimod Natalizumab Mitoxantrone Alemtuzumab Ocrelizumab Cladribine GA Interferons Azathioprine Teriflunomide DF	1. Initial EHT: fingolimod, natalizumab, mitoxantrone, alemtuzumab, ocrelizumab, or cladribine 2. Initial therapies in ESC: GA, interferons, azathioprine, teriflunomide or DF for ≥ 1 year before escalating to high efficacy therapies 3. Disability progression: mean annual EDSS changes from baseline 4. Before propensity score matching took place, patients in the EHT group were associated with older age at first DMT use, shorter disease duration until first DMT use, and more disability.[55] 5. Outcomes measured at 1-10 years follow-up (median follow-up 8.5 years)	1. EHT had lower rates of disability progression at 1-10 years of follow-up (mean delta-EDS differences between groups increased from 0.1 at 1 year to 0.30 at 5 years to 0.64 at 8 years to 0.67 at 10 years) 2. Median time to escalation in ESC group was 6.3 years	1. Limited rationalization for DMT escalation 2. Median time to escalation to high efficacy therapies significantly delayed when compared to contemporary standards 3. Lack of safety outcomes

ß: ß estimate, DF: dimethyl fumarate, DMTs: disease modifying therapies, EDSS: expanded disability status scale, ESC: escalation, EHT: early highly effective treatment, GA: glatiramer acetate, HR: hazard ratio, MRI: magnetic resonance imaging, SAD: sustained accumulation of disability, SPMS: secondary progressive MS, vs: versus

Table 3:

Table 3: RCTs Comparing Approaches		
	DELIVER-MS (NCT03535298)[61]	TREAT-MS (NCT03500328)[62-63]
Sample Size	400	900
Primary Outcome	Whole brain volume loss	Time to sustained disability progression using EDSS plus
Additional outcomes	Clinical assessments, cognitive testing, other MRI results, and patient reported outcomes	Clinical assessments, cognitive and ophthalmologic testing, MRI results, and patient reported outcomes
Timeline	Up to 36 months follow-up	Up to 63 months follow-up
EHT Definition	Alemtuzumab, natalizumab, rituximab, or ocrelizumab	Natalizumab, alemtuzumab, ocrelizumab, rituximab, ofatumumab, or cladribine
Reason to ESC	Based on clinical and/or MRI activity, side effects, or convenience after receiving an initial dose of the low-moderate efficacy medication	Based on evidence of breakthrough disease activity (unspecified). Patients will be re-randomized to escalate to either a high efficacy therapy or another low-moderate efficacy therapy with a different mechanism of action
Additional Observational Cohort Data	Yes	No

EDSS plus: expanded disability status scale that includes EDSS change OR 20% worsening on timed 25-foot walk test or nine-hole peg test that is sustained 6 months later, EHT: early highly effective treatment, ESC: escalation, MRI: magnetic resonance imaging, RCT: randomized control trial