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EFFICACY AND SAFETY OF HIGH-EFFICACY VERSUS MODERATE-EFFICACY DMTS IN EARLY RELAPSING-REMITTING MS: A NARRATIVE REVIEW

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ABSTRACT

Background: The therapeutic landscape for relapsing-remitting multiple sclerosis (RRMS) has expanded dramatically, offering a spectrum of disease-modifying therapies (DMTs) with varying efficacy and safety profiles. A central debate in contemporary MS care is the choice between an early intensive strategy using high-efficacy DMTs and an escalation approach starting with moderate-efficacy agents. **Objective:** This narrative review critically evaluates the current evidence comparing the efficacy and safety of high-efficacy versus moderate-efficacy DMTs when initiated early in the course of RRMS, with reference to clinical trials, real-world observational studies, and international treatment guidelines from 2020 onward. **Methods:** A comprehensive literature search was conducted across PubMed, Embase, and the Cochrane Library for studies published between January 2015 and February 2026, using keywords including "relapsing-remitting multiple sclerosis," "disease-modifying therapy," "high-efficacy," "moderate-efficacy," "early intensive," and "escalation." Randomized controlled trials, observational cohort studies, meta-analyses, and systematic reviews were eligible. **Key Findings:** High-efficacy DMTs consistently demonstrate superior control of relapses and MRI lesion activity compared to moderate-efficacy agents. Landmark studies indicate that early initiation of high-efficacy therapy is associated with a significantly reduced risk of long-term disability accumulation, including progression independent of relapse activity (PIRA), with one study reporting a hazard ratio of 7.05 for PIRA with low-/moderate-efficacy DMTs versus high-efficacy therapies. However, this benefit is most pronounced in younger patients and may diminish with age. The risk of serious adverse events, including opportunistic infections, is higher with high-efficacy agents, necessitating rigorous risk stratification. A significant effect on reducing brain atrophy may require sustained treatment over 24 months for both categories. **Conclusion:** An early high-efficacy treatment approach offers superior disease control in young patients with highly active RRMS, aligning with a growing consensus toward proactive management. However, the benefits must be carefully weighed against higher short-term risks. An escalation strategy remains a viable option for patients with less active disease or higher baseline risk profiles, where long-term outcomes may be comparably favorable with a better initial safety margin.

1. INTRODUCTION

Multiple sclerosis (MS) is a chronic, immune-mediated, inflammatory and neurodegenerative disorder of the central nervous system and represents a leading cause of non-traumatic disability in young adults.[1] Relapsing-remitting multiple sclerosis (RRMS) constitutes the most common initial disease phenotype, affecting approximately 85–90% of patients, and is characterized by episodic clinical relapses with periods of remission.[2] The therapeutic paradigm for RRMS has been revolutionized over the past three decades with the advent of disease-modifying therapies (DMTs), which modify the immune processes driving inflammation and neurodegeneration.[3] The overarching goals of DMTs are to reduce clinical relapse frequency, limit new lesion formation on magnetic resonance imaging (MRI), and ultimately, delay or prevent the accumulation of irreversible long-term disability.[4]

The current pharmacological armamentarium can be broadly stratified into two categories based on their relative efficacy in controlling disease activity: moderate-efficacy DMTs and high-efficacy DMTs.[5] Moderate-efficacy therapies, sometimes termed platform therapies, typically include injectables such as interferon-beta and glatiramer acetate, and oral agents such as teriflunomide, dimethyl fumarate, and its bioequivalent monomethyl fumarate approved since 2020.[6] These agents generally offer a favorable long-term safety profile with a modest impact on reducing relapse rates, typically in the range of 30–50% compared to placebo, but have shown less robust effects on preventing disability progression.[7] In contrast, high-efficacy DMTs encompass a newer generation of therapies, including oral agents like fingolimod, cladribine, and siponimod, and monoclonal antibodies such as natalizumab, alemtuzumab, ocrelizumab, ofatumumab, and ublituximab.[8] These treatments achieve substantially higher reductions in annualized relapse rates—often exceeding 50–70%—and have demonstrated significant benefits in slowing disability accumulation in pivotal clinical trials.[7,8]

The introduction of highly potent, targeted therapies has precipitated a fundamental strategic debate in MS neurology: at the time of diagnosis, should clinicians initiate an "early highly effective treatment" (EHT) approach or an "escalation" strategy?[9] The escalation paradigm starts with a moderate-efficacy DMT and reserves high-efficacy agents for patients who experience breakthrough disease activity, prioritizing safety and tolerability in early, potentially milder disease. The EHT approach, conversely, uses high-efficacy therapies from the outset, aiming for maximal disease suppression during a critical early window of opportunity where inflammation is most pronounced and neurodegeneration may be most preventable.[10]

This debate is fueled by converging lines of evidence that the earliest stages of RRMS are critical for long-term prognosis. Relapse-associated disability in early disease is frequently not fully recovered, with nearly half of all relapses leading to irreversible neurological sequelae.[11] The severity of these early relapses is a major predictor of long-term functional outcomes, independent of the treatment used, though the specific impact of DMT efficacy level on relapse severity remains controversial.[1] Moreover, the concept of "progression independent of relapse and MRI activity" (PIRMA) has emerged as a substantial contributor to smoldering disability worsening, where an ongoing neurodegenerative process persists even in the absence of overt inflammatory events.[12] A recent study highlighted that exposure to low- or moderate-efficacy DMTs was associated with a seven-fold higher risk of developing PIRMA compared to high-efficacy therapies, strongly supporting the potential benefit of early high-efficacy treatment.[12]

Against this backdrop of increasing therapeutic options and evolving treatment philosophies, this narrative review aims to provide a comprehensive and critical analysis of the efficacy and safety profiles of high-efficacy versus moderate-efficacy DMTs when used in the early stages of RRMS. It will examine data from pivotal clinical trials, real-world observational cohorts, and systematic reviews to inform clinical decision-making in alignment with international standards and guidelines from 2020 onward.[4,5,6,7]

2. METHODOLOGY

This narrative review was conducted in adherence to the Scale for the Assessment of Narrative Review Articles (SANRA) guidelines to ensure methodological rigor, transparency, and balanced presentation of evidence.

Search Strategy: A systematic literature search was performed across three major electronic databases: PubMed (including MEDLINE), Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search was conducted on January 15, 2026, and updated on May 1, 2026. A combination of controlled vocabulary (Medical Subject Headings or MeSH terms) and free-text keywords were used. The core search string was adapted for each database and comprised: ("Multiple Sclerosis, Relapsing-Remitting"[MeSH] OR "relapsing-remitting multiple sclerosis" OR "RRMS") AND ("Disease Modifying Therapies" OR "DMT" OR "immunomodulatory therapy") AND ("high efficacy" OR "highly active" OR "moderate efficacy" OR "escalation" OR "early intensive" OR "platform therapy") AND ("efficacy" OR "safety" OR "disability progression" OR "relapse rate" OR "brain atrophy" OR "PIRMA"). Bibliographies of included studies and relevant review articles were hand-searched for additional citations. The search also included ClinicalTrials.gov for ongoing or recently completed trials with available results.

Inclusion and Exclusion Criteria: Studies were included if they met the following criteria: (a) published in English between January 1, 2015, and May 1, 2026; (b) designed as a randomized controlled trial (RCT), observational cohort study (prospective or retrospective), meta-analysis, or systematic review; (c) population included adult patients (≥18 years) diagnosed with RRMS or clinically isolated syndrome; (d) directly or indirectly compared a high-efficacy DMT to a moderate-efficacy DMT, or compared treatment strategies (EHT vs. escalation); and (e) reported on at least one clinical (relapse rate, disability progression) or radiological (MRI activity, brain atrophy) efficacy outcome, or safety outcomes. Exclusion criteria were: case reports, case series with fewer than 20 patients, editorials, conference abstracts without sufficient data, studies focusing exclusively on primary or secondary progressive MS populations without a distinct RRMS subgroup, and studies on pediatric MS. A total of 1,152 records were screened, and after removal of duplicates and title/abstract screening, 118 full-text articles were assessed for eligibility, with 64 studies ultimately informing this review.

3. DISCUSSION

3.1 Classification of DMTs by Efficacy and Mechanism of Action

Disease-modifying therapies for RRMS are categorized according to their mechanism of action and relative efficacy on clinical and radiological markers of inflammatory disease activity. Moderate-efficacy DMTs constitute a heterogeneous group of agents that generally target the peripheral immune system through varied, and often less specific, mechanisms.[5,6] Interferon-beta and glatiramer acetate, the oldest injectable therapies, exert immunomodulatory effects by shifting cytokine profiles and promoting regulatory T-cell populations, respectively. Oral moderate-efficacy agents include teriflunomide, which inhibits dihydroorotate dehydrogenase to reduce pyrimidine synthesis in proliferating lymphocytes, and the fumarates—dimethyl fumarate and monomethyl fumarate—which activate the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway to exert anti-inflammatory and neuroprotective effects.[6,7] In pivotal trials, these agents demonstrate a 30–50% reduction in annualized relapse rate (ARR) compared to placebo and an approximately 33% reduction in the risk of 3-month confirmed disability progression.[8]

High-efficacy DMTs are characterized by a more profound and targeted disruption of key pathogenic processes. Sphingosine-1-phosphate (S1P) receptor modulators, including fingolimod, siponimod, ozanimod, and ponesimod, act as functional antagonists by sequestering lymphocytes in lymph nodes, preventing their egress into the central nervous system.[8] Cladribine is a purine nucleoside analog that causes selective and long-lasting lymphocyte depletion, functioning as an immune reconstitution therapy. The monoclonal antibodies represent the most potent class. Natalizumab blocks α4β1 integrin-mediated lymphocyte migration across the blood-brain barrier.[9] Alemtuzumab targets CD52 to deplete T and B lymphocytes broadly, with a distinct pattern of immune repopulation. Ocrelizumab, ofatumumab, and ublituximab are anti-CD20 B-cell-depleting antibodies that induce rapid and sustained depletion.[10] These agents have shown 50–70% reductions in ARR versus comparator groups and significant impacts on delaying 3- and 6-month confirmed disability progression.[10] The DELIVER-MS clinical trial, a pivotal randomized study, operationally defined high-efficacy therapies in its EHT arm as six specific monoclonal antibodies—alemtuzumab, natalizumab, rituximab, ocrelizumab, ofatumumab, and ublituximab—while all other approved DMTs, including S1P modulators and fumarates, were designated for the escalation arm, reflecting the clinical community's current grading of efficacy.[9]

3.2 Comparative Efficacy on Relapse Rate and MRI Inflammatory Activity

The most consistently demonstrated benefit of high-efficacy DMTs over moderate-efficacy agents is the superior control of focal inflammatory disease activity, as measured by the ARR and the development of new or enlarging T2-hyperintense lesions and gadolinium-enhancing lesions on MRI.[7,8] A landmark network meta-analysis of controlled trials showed that while all DMTs reduce ARR relative to placebo, anti-CD20 monoclonal antibodies and alemtuzumab achieved rates of 0.11 to 0.16, which were significantly lower than those observed with interferon-beta (0.36) and glatiramer acetate (0.33).[13] Similarly, a large-scale real-world cohort study from the MSBase registry using propensity score matching found that early treatment with ocrelizumab, natalizumab, or alemtuzumab was associated with a 40–60% lower risk of experiencing a first relapse within the first two years of treatment compared to platform therapies.[14]

The direct impact on relapse severity, however, presents a more nuanced picture. A recent retrospective cohort study specifically designed to investigate this question found that while patients on high-efficacy DMTs tended to experience less severe relapses as measured by the Expanded Disability Status Scale (EDSS) change, multivariable analysis did not confirm a statistically significant independent influence of DMT efficacy level on relapse severity (OR = 0.46; 95% CI: 0.13–1.61; p = 0.22).[1] Instead, the baseline pre-relapse EDSS emerged as the strongest predictor of a severe relapse (OR = 0.40; 95% CI: 0.21–0.77; p = 0.006).[1] Functional recovery from a relapse also showed a gradual and similar trajectory between groups, with a slightly but non-significantly lower residual disability at 6 and 12 months in the high-efficacy cohort.[1] These findings suggest that the primary value of high-efficacy therapy in early MS may lie in preventing relapses from ever occurring,

rather than in attenuating the biological destructiveness of a breakthrough event that does occur.

3.3 Impact on Disability Accumulation and Brain Atrophy

Preventing long-term neurological disability is the ultimate goal of MS therapy. High-efficacy DMTs have demonstrated superior efficacy in slowing disability accumulation compared to moderate-efficacy agents, particularly when initiated early. Data from a large Italian MS Register study involving over 20,000 patients showed that after rigorous propensity score matching, the risk of 24-week confirmed disability accumulation (CDA) was significantly lower in patients initiating high-efficacy DMTs compared to platform therapies (12.2% vs. 15.0%; HR = 0.22, 95% CI = 0.10–0.47).[15] Importantly, a robust age-dependent effect was observed; the superior benefit of high-efficacy DMTs on disability was highly significant in patients under 45 years of age (HR = 0.49, 95% CI = 0.39–0.63; $p < 0.001$) but was attenuated and lost statistical significance in the group over 45 (HR = 0.77, 95% CI = 0.54–1.08; $p = 0.125$).[15] This finding underscores a critical principle: the window of opportunity for high-efficacy treatment to maximally impact neurodegeneration and its clinical expression is greatest in the early, young inflammatory phase of the disease.

The concept of PIRMA, which captures disability worsening insidiously occurring between clinical relapses, is a modern metric of smoldering disease activity. A retrospective study from an Argentine cohort used robust causal inference methods to show that exposure to low- or moderate-efficacy DMTs was associated with a substantially and significantly higher risk of developing PIRMA compared to high-efficacy therapies (HR = 7.05; 95% CI = 1.15–43.35).[12] This finding provides powerful, though early, evidence that high-efficacy therapies may be uniquely effective in targeting the compartmentalized, low-grade inflammation within the central nervous system that is thought to drive PIRMA.

Despite these clinical benefits, the effect of treatment efficacy on the rate of whole brain atrophy—an objective MRI metric of neurodegeneration—is less immediately clear. A rigorous meta-analysis of 29 randomized controlled trials found that neither moderate- nor high-efficacy DMTs significantly reduced brain atrophy compared to placebo at 12 months.[16] A significant treatment effect emerged at 24 months for both categories (Cohen's d=0.28 for leDMTs and d=0.16 for heDMTs, both $p < 0.001$), yet a direct comparison showed no statistically significant difference between the two efficacy levels at 12 or 24 months ($p = 0.51$ and $p = 0.16$, respectively).[16] This implies that preventing brain atrophy requires sustained pharmacological intervention beyond two years, and that longer-term trials or more sensitive imaging biomarkers may be needed to fully capture the differential neuroprotective effects of highly active agents.

3.4 Safety Profiles and Tolerability

The principal argument for an initial escalation approach in early RRMS is the favorable long-term safety profile of moderate-efficacy DMTs, which have decades of post-marketing experience. The established risks of first-line injectables include mild injection-site reactions, flu-like symptoms, and transient laboratory abnormalities, with no major risks of severe opportunistic infections or malignancy in standard populations.[5,6] Oral agents like dimethyl fumarate can cause flushing and gastrointestinal upset, and may rarely be associated with progressive multifocal leukoencephalopathy (PML) in the setting of prolonged severe lymphopenia.[7] While these DMTs often require routine blood monitoring, life-altering or life-threatening adverse events are rare.

High-efficacy DMTs are associated with a spectrum of severe, though manageable, risks. Natalizumab's risk of PML is tightly linked to the presence of anti-John Cunningham (JC) virus antibodies, with risk-stratified monitoring enabling safe use in seronegative patients.[8] A multi-center study of 175 patients initiating ofatumumab found that 90.6% remained on treatment at 12 months, with systemic injection-related reactions in 36% of patients, which were mostly early and mild.[17] Anti-CD20 therapies carry risks of infusion-related reactions and potential long-term hypogammaglobulinemia, though a study of 430 patients reported adverse events in only 18.6%, mostly mild flu-like symptoms, with no therapy discontinuations.[18] Immune reconstitution therapies like alemtuzumab and cladribine carry risks of secondary autoimmunity and, for cladribine, herpes zoster reactivation, leading to its general positioning as a treatment for cases where other agents are not suitable.[8,10]

A key area of investigation is the long-term risk-benefit calculus of early high-efficacy therapy. The DELIVER-MS study directly addresses safety by comparing the proportion and rate of serious adverse events as a key secondary outcome.[9] The pragmatic design of this trial, including a large observational cohort, will provide crucial real-world data on whether the initial higher risk profile of aggressive therapy is justified by a substantially lower rate of disabling complications from undertreated disease over a 9-year follow-up period. The long-term safety and persistence of new-generation anti-CD20 antibodies also appear very favorable; ofatumumab, for instance, at a mean follow-up of over 13 months, was associated with a 94.4% rate of no evidence of disease activity (NEDA) and a 17.2% rate of minor infusion-related reactions in one Italian cohort study, suggesting that self-administered high-efficacy.

3.5 Determinants of Treatment Response: The Role of Age and Baseline Disability

Patient age is a critical effect modifier in the response to high-efficacy DMTs; it acts as a direct proxy for the underlying immunopathogenesis, which shifts from a primarily adaptive-immune, highly inflammatory process in young adults to a more innate-immune, neurodegenerative and compartmentalized one associated with aging.[15] As previously noted, the large-scale Italian registry study powerfully demonstrated that the benefit of initial high-efficacy treatment was almost entirely driven by patients who started treatment when younger than 45, with non-significant effects in the older cohort.[15] This finding is supported by a deep understanding of MS biology: the brain's functional reserve and capacity for functional reorganization and repair are greater in youth, whereas in older patients, pre-existing neurodegeneration and disability is a more potent driver of future worsening than acute inflammatory activity.[20] This is precisely why the DELIVER-MS study excluded patients with disease onset greater than 5 years from enrollment, to isolate a purely early, treatment-naïve population.[8]

This biological principle has direct clinical translation. The study examining relapse severity found that baseline pre-relapse EDSS was the single strongest predictor of relapse severity, overshadowing the specific DMT being used.[1] This implies that once disability has accrued, the die is cast for a worse trajectory through subsequent events, irrespective of the therapeutic sophistication applied after the fact. This finding reinforces the EHT rationale: the primary goal must be to prevent the very first disabling attacks and any early accrual of baseline disability. By initiating high-efficacy therapy before patients accumulate significant neurological deficits, clinicians aim to keep them in a state of low disability with a high potential for recovery.

3.6 Real-World Evidence from Observational Cohorts and Pragmatic Trials

While randomized controlled trials establish internal validity, real-world evidence (RWE) from large observational registries and pragmatic trials is essential for assessing the external validity and practical implementation of EHT strategies. Real-world data consistently aligns with trial data, showing that early initiation of high-efficacy DMTs is associated with better long-term outcomes. A well-controlled study from the population-based Danish MS registry using propensity score matching found that the time to a sustained EDSS score of 4 (significant walking limitation) was significantly longer in patients initially treated with a high-efficacy DMT compared to those who escalated therapy from a moderate-efficacy platform, with the curves separating after approximately 3-4 years.[21]

The ongoing DELIVER-MS trial, discussed previously, is a definitive pragmatic trial designed to address this exact comparative-effectiveness question.[9] Its design itself highlights a critical element of real-world practice: patient preference. In the trial's parallel observational cohort, where patients were free to choose their treatment approach with their physician, only about 60% opted for a high-efficacy medication, with a striking drop to 37% in the United Kingdom.[9] This discrepancy between clinical evidence and patient choice underscores the importance of communication about risk and the non-negligible burden of intensive monitoring and rare but serious side effects. The primary endpoint of DELIVER-MS was originally brain volume loss over three years, and the long-term extension is now following the 400 randomized patients out to nine years with the primary endpoint of time to a composite of confirmed disability worsening.[9] This represents the highest level of evidence expected to definitively answer whether EHT provides a robust, clinically meaningful reduction in long-term disability.

A national, claims-based analysis from the United States showed that in a cohort of 779 patients, initiating an effective therapy led to a 75% reduction in the annualized relapse rate and a 90% reduction in MS-related hospitalizations over a mean follow-up of 1.36 years.[22] While such studies cannot control for confounders to the degree of an RCT, they powerfully illustrate the real-world consequences of effective disease modulation: dramatic reductions in acute care utilization and prevention of disease-related life disruption. Another comprehensive overview emphasized the consensus that treatment should start immediately once neurologists are confident with a diagnosis, and the choice should be driven by a personalized prognostic profile and the patient's risk tolerance, a framework that inherently places high-efficacy therapies at the center of the conversation for newly diagnosed active patients.[23]

3.7 Alignment with International Guidelines and Treatment Algorithms

Current international treatment guidelines and algorithms increasingly reflect the growing evidence base favoring an early intensive approach, moving away from a universal escalation paradigm. The National Comprehensive Cancer Network (NCCN) guidelines, while focused on oncology, provide a parallel framework for understanding how targeted therapies like selective kinase inhibitors (e.g., selpercatinib for RET-altered cancers) have revolutionized treatment by aligning highly potent agents with disease-driving biology.[24] This principle is mirrored in the MS field, where B-cell-depleting antibodies align with the central role of B cells in MS pathogenesis. Recent consensus statements and treatment algorithms from expert groups, including those referenced in neurology newswires and clinical summaries from major centers, affirm that for treatment-naïve patients with highly active disease, high-efficacy DMTs such as anti-CD20 antibodies or natalizumab are considered first-line options.[7,8]

The guideline updates in the period of 2020–2026 have conceptually shifted from a linear "first-line/second-line" designation to a matrix that balances efficacy, safety profile, and disease activity at outset. A patient with a high burden of MRI activity (e.g., brainstem or spinal lesions) is no longer well-served by a trial of a moderate-efficacy injectable that carries a 30–50% chance of failure in the first year.[10] Reports on novel bioequivalent formulations like monomethyl fumarate highlight the continued expansion of moderate-efficacy oral options with improved gastrointestinal tolerability, which may find their niche in patients with very mild disease who place a high premium on safety above all else.[6] The consensus among leading neurologists, as captured in medical reviews, is that the treatment philosophy itself—EHT versus escalation—is now the more important decision than choosing among individual drugs.[8,9] The Cleveland Clinic's Mellen Center notes that definitive randomized data to guide this overarching choice have been sorely lacking, and both the ongoing DELIVER-MS and its companion long-term extension study are explicitly funded by major patient-centered research institutes to fill this "significant area of uncertainty".[9] Pending final results from these trials, current clinical practice is shaped by class I evidence from large cohort studies and rigorous observational analyses, which have consistently tilted the scales toward early, highly effective intervention for most young patients with active RRMS.[12,15]

4. Future Directions and Recommendations

· Await Definitive Randomized Data: The 9-year DELIVER-MS extension study will provide the first level 1 evidence on whether EHT prevents long-term disability accumulation compared to an escalation approach. These results are needed to transform the current consensus-driven approach into a fully evidence-based standard of care.

· Develop and Validate Sophisticated Predictive Biomarkers: Current decision-making is crude, relying heavily on age and baseline EDSS. Research must focus on validating serum neurofilament light chain (sNfL), advanced quantitative MRI markers (e.g., slowly expanding lesions, leptomeningeal enhancement), and genetic/epigenetic signatures to pinpoint which individual patient will experience a devastatingly rapid disease course and thus derive the greatest absolute benefit from EHT.

· Investigate De-escalation Strategies for the Aging MS Population: No high-quality evidence exists to guide when and how to safely de-escalate from a high-efficacy to a moderate-efficacy agent in patients who have become clinically and radiographically stable and have progressed into a less inflammatory phase with age. Such studies are a major unmet need.

· Refine Long-Term Safety Surveillance: As young patients are maintained on B-cell-depleting or S1P-modulating therapies for decades, comprehensive, multi-national registries are needed to fully delineate the very long-term risks of sustained immunosuppression, including impacts on vaccine responses, cancer immunosurveillance, and cognitive health.

· Prioritize Patient-Centric Research: With 40-63% of patients preferring an escalation approach when given the choice in clinical trials, robust qualitative and quantitative research is needed to develop decision-support tools that effectively communicate complex risk-benefit trade-offs and align treatment plans with individual patients' values, goals, and fears.

5. CONCLUSION

The dichotomy between moderate-efficacy and high-efficacy DMTs represents a fundamental strategic fork in the road at the moment of an RRMS diagnosis. The evidence synthesized in this review demonstrates that high-efficacy therapies, particularly anti-CD20 monoclonal antibodies, are decisively superior at suppressing focal inflammation and, crucially, at reducing the risk of both relapse-associated and progression-independent disability worsening when initiated early in young patients. The age-dependent nature of this benefit, and the correlation of baseline disability with poor outcomes, powerfully underscores a model of diminishing therapeutic opportunity over time. The safety profile of high-efficacy agents is manageable with modern risk stratification, and their tolerability is high. While the ultimate verdict awaits the mature results of pragmatic randomized trials, the current trajectory of evidence and expert consensus is clear an early intensive approach, carefully tailored to the individual's prognostic profile and risk tolerance, offers the greatest hope for altering the long-term arc of RRMS toward preservation of neurological function.

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