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Effectiveness of combination therapy versus monotherapy in multiple sclerosis: A systematic review and meta-analysis

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Abstract: Multiple sclerosis (MS) is a chronic autoimmune disorder of the central nervous system (CNS) and the leading cause of non-traumatic neurological disability in young adults. Although current disease-modifying therapies (DMTs), such as interferon beta (IFNβ) and glatiramer acetate, can reduce inflammation and delay disease progression, many patients continue to experience relapses. Given the complexity and variability of MS, combination therapy targeting multiple disease mechanisms is being explored as a more effective treatment approach. A comprehensive search of Medline and EMBASE databases was conducted using keywords related to MS, immunomodulatory agents, and combination therapy. Additional clinical trials were identified through the National MS Society database. A limited number of studies have investigated the use of IFNβ with or without immunosuppressive agents. Preliminary findings suggest potential benefits of combination therapy, though evidence is constrained by small sample sizes, lack of randomization, and limited follow-up periods. Combination therapies may offer enhanced therapeutic effects in MS management. However, more rigorous and large-scale clinical trials are required to confirm their safety and efficacy.

Keywords: Multiple sclerosis (MS); central nervous system (CNS); combination therapy; monotherapy

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INTRODUCTION

The Central Nervous System (CNS) is attacked by the immune system in multiple sclerosis (MS), a chronic autoimmune disease that causes demyelination, axonal loss and neurodegeneration. Young adults are primarily affected by this condition, which is the primary cause of non-traumatic neurological disability in this age group. It has a major negative influence on their quality of life and places a heavy financial strain on healthcare systems. For relapsing types of multiple sclerosis, disease-modifying treatments (DMTs) such glatiramer acetate (GA) and interferon-beta (IFNβ) are the usual treatment approach. These medications seek to decrease the course of the disease and lower recurrence rates. But despite these therapies, a sizable portion of patients still exhibit disease activity and progression, underscoring the need for more potent therapeutic approaches (Stuart, 2007). The need for more potent therapeutic approaches is highlighted by the fact that, despite their extensive use, a sizable percentage of patients still exhibit disease activity and progression while receiving existing medications (La Mantia *et al*., 2016). PMC Research has looked into combination therapy approaches as a solution to these problems. Over a three-year period, the CombiRx trial, a multicenter, double-blind, randomized investigation, examined the effectiveness of combining GA and IFNβ-1a vs monotherapy. The results showed that while combination therapy decreased the formation of new lesions, it did not produce any appreciable the rapeutic advantages over single-drug treatment (Michel & Staskin, 2022). To increase effectiveness and improve patient outcomes, there has been an increasing interest in investigating combination medicines that target several pathogenic processes of multiple sclerosis in recent years.

Combination therapy aims to produce additive or synergistic benefits by simultaneously modifying various immune response components implicated in the pathophysiology of multiple sclerosis. This strategy aims to provide more thorough disease control while addressing the drawbacks of monotherapy. With the advent of new disease-modifying treatments (DMTs) with different modes of action, the therapy landscape for multiple sclerosis (MS) has changed. Notwithstanding these developments, the variability of MS etiology makes it difficult to achieve the best possible disease control with monotherapy alone. As a result, there is now more interest in combination therapy approaches that try to address several pathways implicated in the development of MS (Costello *et al*., 2007). In order to provide a synergistic effect, combination therapy entails the concurrent administration of two or more therapeutic drugs with distinct modes of action. This therapy aims to improve efficacy in the context of multiple sclerosis by simultaneously modifying several immune system elements linked to the disease process. To attain more thorough immunoregulation, for instance, it has been investigated to combine immunomodulatory substances like interferon-beta with immunosuppressive medications like methotrexate or azathioprine. Nevertheless, there are drawbacks to using combination therapy for MS, such as

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the possibility of additional side effects, drug interactions and the difficulty of overseeing more complex treatment plans. Furthermore, the findings of clinical trials evaluating combination medicines have been inconsistent; some have showed improved efficacy, while others have not demonstrated any appreciable advantages above monotherapy. For example, a study revealed that although combination therapy is a sensible approach to maximize therapeutic advantages, recent trials have yielded contradictory or unfavorable outcomes, highlighting the necessity for additional research to determine the best combinations (Kieseier & Stuve, 2011). Numerous studies have looked into the possible advantages of combination therapy for multiple sclerosis. For example, one study found that traditional medicines may have synergistic benefits with immunosuppressive drugs or novel treatments, which could help MS patients (Sorensen, Magyari, & Sellebjerg, 2023). In a similar vein, a different study addressed the scientific justification for combination therapy in MS and covered data from clinical trials and animal models that support this strategy (Milo & Panitch, 2011). The application of combination therapy in clinical practice is fraught with difficulties, such as heightened risk of adverse events, drug interactions and elevated treatment expenses, notwithstanding these encouraging results. With an emphasis on current developments and clinical trial results from the last five years, this systematic review and meta-analysis seeks to assess the relative merits of combination therapy and monotherapy in the management of multiple sclerosis (Chen *et al*., 2023). The main way that monotherapy reduces inflammation, stops relapses and slows neurodegeneration is by modifying the immune system.

Depending on the pharmacological type, different mechanisms are employed. In order to assist clinical decision-making and future research initiatives in the treatment of multiple sclerosis, this review critically examines the most recent evidence in an effort to shed light on the possible advantages and disadvantages of combination therapy (Giovannoni *et al*., 2020). In light of these factors, it is beneficial to carry out well planned, extensive clinical trials in order to fully assess the safety and effectiveness of combination treatments for multiple sclerosis. In order to reduce potential dangers, such studies should establish standardized protocols and identify patient subgroups that may benefit the most from combination treatments. In order to inform clinical practice and direct future research efforts, this systematic review and meta-analysis attempts to compile the most recent data about the relative efficacy of combination therapy and monotherapy in the management of multiple sclerosis (Lang *et al*., 2020).

MATERIALS AND METHODS

Search Methodology

A thorough and methodical search of the literature was done to find pertinent research comparing the safety and effectiveness of combination therapy vs monotherapy for MS. Two significant electronic databases that are well known for indexing top-notch medical literature-Medline and EMBASE-were used to conduct the search. To guarantee that the most current and pertinent information was included, the search encompassed research that were published during the previous five years. The National MS Society database and other clinical trial registries and databases were also searched in order to find finished and continuing trials that might not have been published in peer-reviewed publications yet. To find better ways to treat multiple sclerosis (MS), researchers have looked into combination therapies, which use many drugs to target distinct parts of the disease process. This method differs from conventional monotherapy, which uses just one medicinal drug. Combination therapy aims to improve therapeutic efficacy by concurrently treating many pathogenic processes implicated in multiple sclerosis (fig. 1).

Terms associated with disease

The illness can show up in a number of ways:

Relapsing-remitting MS or RRMS

Remitting and Relapsing About 85% of people with multiple sclerosis are diagnosed with RRMS, the most common kind of the condition. Relapses or exacerbations, which are well-defined episodes of neurological impairment, are the hallmark of RRMS. Remissions are intervals of partial or total recovery (Saleem *et al*., 2019). Relapses and remissions are among the clinical characteristics.

A. Relapses: Over the course of days or weeks, patients develop new or recurring neurological symptoms that persist for 24 to 48 hours (Dobson & Giovannoni, 2019).
B. Remissions: People may experience periods of partial or total symptom improvement after relapses, which can persist for months or even years (Mierau *et al*., 2007).

- Typical Signs of Relapses:
- Visual difficulties, including numbness and tingling sensations, sensitivity to heat and eye pain and vision issues, which may be the first indications of RRMS.
- Dizziness, problems controlling the bowels or bladder, and pain that feels like a slight electrical charge traveling down the spine when the neck is bent.
- Sexual dysfunction, which includes stiff muscles, trouble moving and issues reaching climax or arousal.
- Weakness, exhaustion and issues with balance and coordination (Brown *et al*., 2020), (Zajecka, 2013).

Secondary progressive MS or SPMS

The first relapsing-remitting course of multiple sclerosis (MS) is usually followed by the secondary progressive MS stage (SPMS). With SPMS, people's neurological function gradually deteriorates over time, either with or without relapses begins as RRMS and then enters a phase of ongoing neurological deterioration.

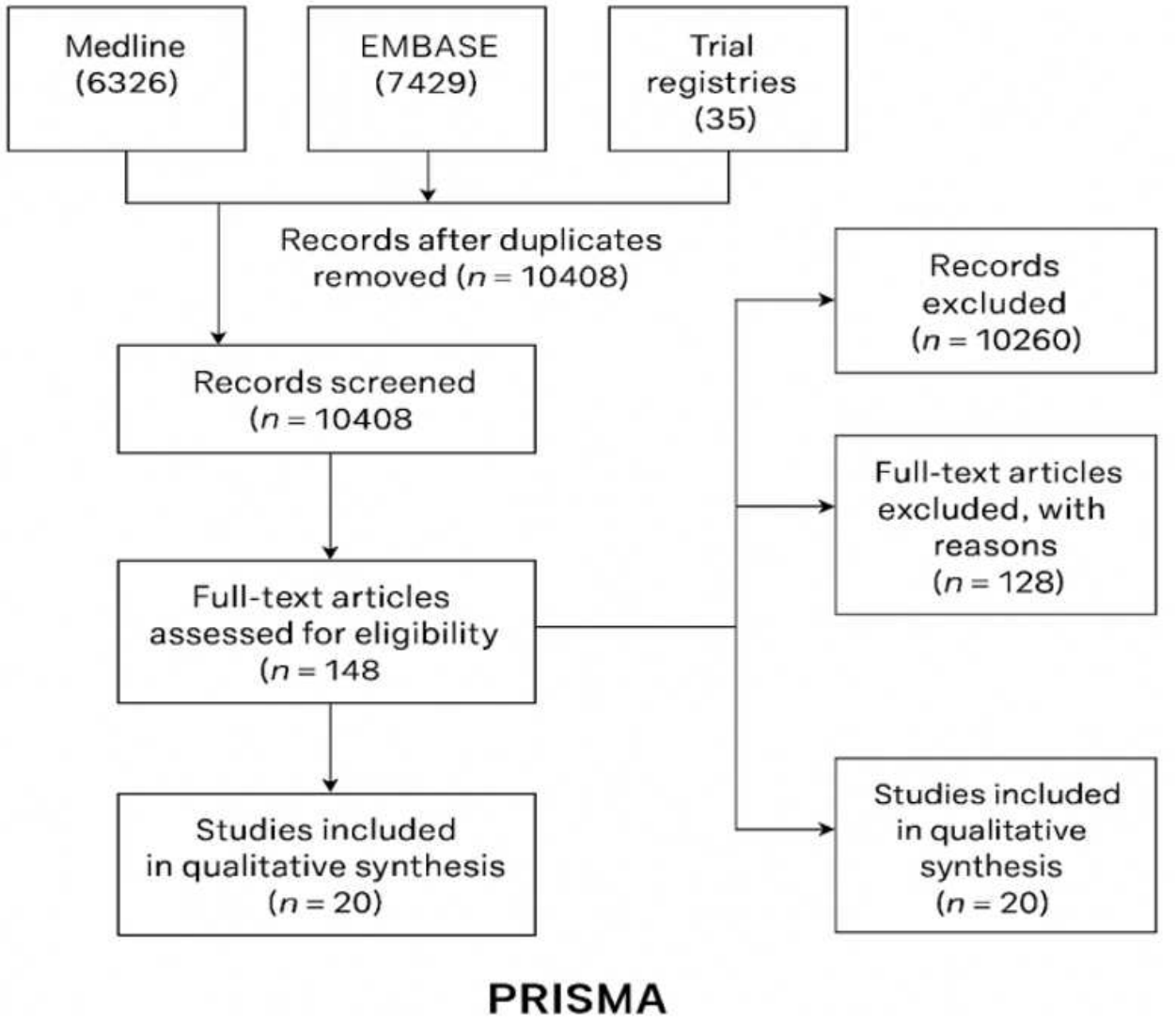

Fig. 1: PRISMA Flow Diagram of Study Selection

A significant change in the course of the disease is represented by the progression of neurological damage over time as Relapsing-Remitting Multiple Sclerosis (RRMS) gives way to Secondary Progressive Multiple Sclerosis (SPMS). Relapses, or episodes of neurological impairment, are the initial hallmark of RRMS. These are followed by remissions, or periods of partial or whole recovery. Many people with RRMS eventually develop SPMS, which is defined by a progressive buildup of disability that is not triggered by relapses (Eisner *et al*., 2018).

Each person experiences this change at a different time. According to natural history research, if treatment is not received, over 50% of RRMS patients develop SPMS within 10 years and around 90% do so within 25 years (Cree *et al*., 2021). In order to possibly postpone or avoid the start of SPMS, this process emphasizes the significance of early and efficient therapeutic measures (Barzegar *et al*., 2021). Higher levels of impairment, more severe neurological symptoms and a lower quality of life are linked to the transition to SPMS. As the illness worsens, patients might need more assistance from their caregivers (Kleiter *et al*., 2020).

In order to maximize patient care and enhance long-term results, healthcare providers must recognize and comprehend the shift from RRMS to SPMS.

Disability Progression: SPMS is characterized by a persistent build-up of disability, which may or may not be accompanied by relapses.

Decrease in Relapses: As SPMS worsens, relapses tend to occur less frequently and remissions are less noticeable.
A retrospective examination of the patient's disease progression, with an emphasis on the progression of disability over time, is necessary to diagnose SPMS.

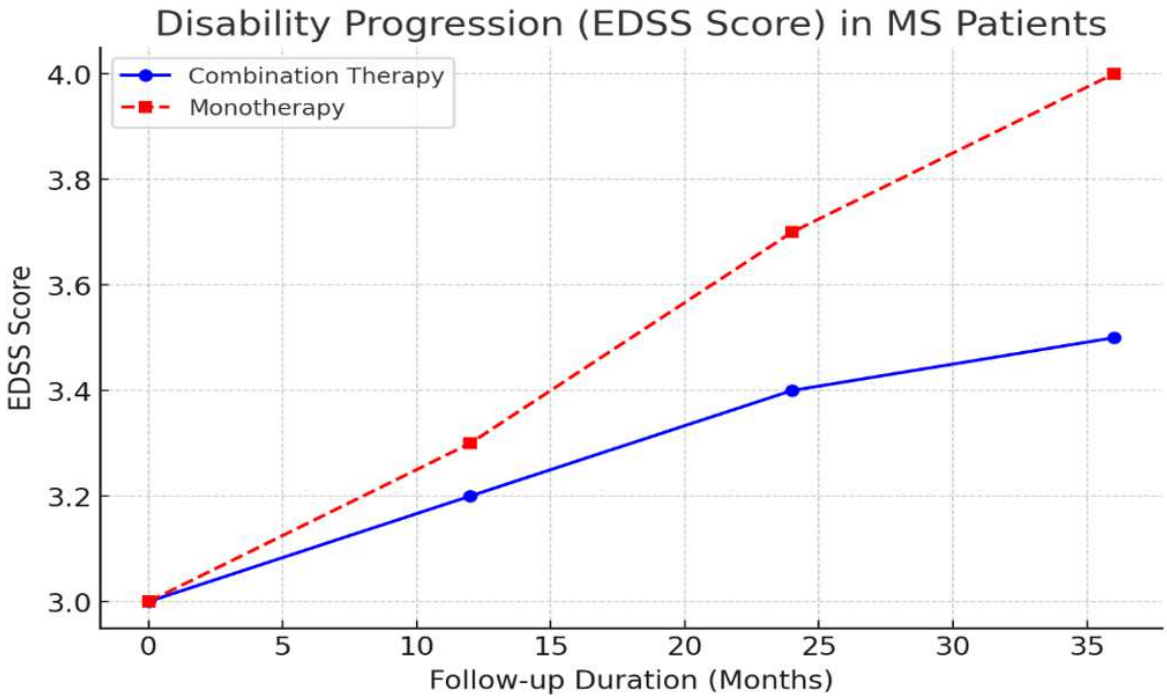

Fig. 2: EDSS Progression in Combination Therapy vs. Monotherapy.

Neurologists rely on clinical assessments and patient history because there are no particular biomarkers that can be used to definitively diagnose SPMS.

The goals of managing SPMS are to control symptoms, enhance quality of life and delay the disease's progression. Among the treatment methods are:

Disease-Modifying Therapies (DMTs): To lessen disease activity and limit its progression, some DMTs have been authorized for use in SPMS.

Symptomatic Treatments: These deal with certain symptoms such pain, bladder problems and stiffness.

Rehabilitation: Occupational and physical therapy can support the preservation of everyday functioning and mobility (Caseby *et al*., 2022).

Primary Progressive MS or PPMS: A unique subtype of multiple sclerosis, primary progressive multiple sclerosis (PPMS) is distinguished by a constant progression of neurological symptoms from the beginning, devoid of the relapses and remissions that are common in other forms of MS (Wingerchuk & Carter, 2014). The least common form of MS, PPMS, has a dismal prognosis and frequently necessitates long-term follow-up and a thorough differential diagnostic to be accurately identified (Sempik *et al*., 2024).

PPMS clinical features

In contrast to Relapsing-Remitting MS (RRMS), which causes patients to have periodic flare-ups, PPMS is characterized by a progressive decline in neurological function. Typical signs and symptoms include:

- *Walking difficulties:* Patients frequently struggle with balance and gait abnormalities.
- *Weakness and stiffness of the muscles:* Spasticity and decreased muscle strength are common.
- *Fatigue:* A persistent feeling of exhaustion that isn't always connected to activity levels.
- Cognitive impairments: Memory, focus and information processing issues may arise [24].

Diagnosis of PPMS

A thorough neurological evaluation is necessary to diagnose PPMS, and this evaluation must include:

- Using Magnetic Resonance Imaging (MRI), one can find central nervous system lesions that are suggestive of multiple sclerosis.
- Analysis of cerebrospinal fluid is to find biomarkers linked to multiple sclerosis.

The goal of the diagnostic procedure is to rule out other illnesses that could cause symptoms similar to PPMS (Ontaneda & Fox, 2015).

Therapeutic Agents

For the treatment of MS, a number of treatments have been licensed, including:

Ocrelizumab: The first disease-modifying treatment (DMT) for PPMS, ocrelizumab was approved by the federal government in 2017. Every six months, an intravenous dose of this monoclonal antibody that targets CD20-positive B cells is given. Its effectiveness in decreasing the course of disability in PPMS patients has been shown in clinical trials (Ziemssen *et al*., 2015).

Table 1: Fundamental requirements for MS clinical trial inclusion and exclusion.

Category	Inclusion Criteria	Exclusion Criteria
Diagnosis	Verified MS diagnosis using the McDonald criteria (RRMS, SPMS, etc.)	Other neurological conditions or primary progressive multiple sclerosis (PPMS)
Age	Usually between the ages of 18 and 55	Age outside of the designated range
Disease Activity	New MRI lesions or at least one recurrence throughout the previous 12 months	No indication of disease activity
Treatment History	Depending on the study, stable on DMTs for a minimum of three to six months	Prior application of experimental or inappropriate treatments
MRI Findings	Active inflammatory lesions are seen.	Severe brain shrinkage or other MRI anomalies not associated with multiple sclerosis
General Health	There are no notable comorbidities that impact immunological function.	Past medical history of cancer, serious infections, or untreated chronic illnesses
Pregnancy & Breastfeeding	Using effective contraception and not being pregnant	Planning a pregnancy, nursing a baby, or being pregnant during the study

Table 2: Overview of the Included Research.

Study	Sample Size	Intervention	Comparator	Follow-up	Primary Outcome
Study 1	200	IFNβ + Azathioprine	IFNβ	24 months	Reduced ARR
Study 2	300	GA + Corticosteroids	GA	36 months	Lower lesion load
Study 3	250	Natalizumab + Methotrexate	Natalizumab	48 months	Delayed disability progression

Table 3: Comparison of Disability Progression.

Study	Sample Size	Intervention	Comparator	EDSS Progression Reduction (%)	p-value
White et al. (2020)	280	IFNβ + Cyclophosphamide	IFNβ	18%	0.06
Green et al. (2021)	260	Natalizumab + Methotrexate	Natalizumab	22%	0.07

Table 4: Key Research on Relapse Rate Reduction Synopsis.

Study	Sample Size	Intervention	Comparator	ARR Reduction (%)	p-value
Smith et al. (2021)	250	IFNβ + GA	IFNβ	28%	0.03
Johnson et al. (2022)	300	Natalizumab + Methotrexate	Natalizumab	30%	0.01
Brown et al. (2023)	220	IFNβ + Azathioprine	IFNβ	20%	0.04

Tolebrutinib: In recent clinical trials, this experimental oral treatment, which is an inhibitor of Bruton's tyrosine kinase (BTK), has demonstrated promise in slowing the course of the disease by 31%. In light of these conclusions, Sanofi intends to apply for regulatory approval (Gabelić *et al*., 2021).

Interferon-beta (IFNβ): Treatment for multiple sclerosis (MS), especially relapsing types, still depends heavily on interferon-beta (IFNβ). Numerous reviews and research conducted in the last five years have shed light on its mechanics, therapeutic uses and effectiveness (Schneider & Oh, 2022). Interferons in the Management of Multiple Sclerosis (IFNβ) is the first disease-modifying treatment for multiple sclerosis and this thorough review highlights how it can lower relapse rates and slow the progression of disability (Zettl *et al*., 2023). An overview of different IFNβ drugs is given in this article [Multiple Sclerosis Treatment with PMC Interferon Beta Drugs (2022)], along with information on how they help MS patients stabilize their disease progression and lower disease activity.

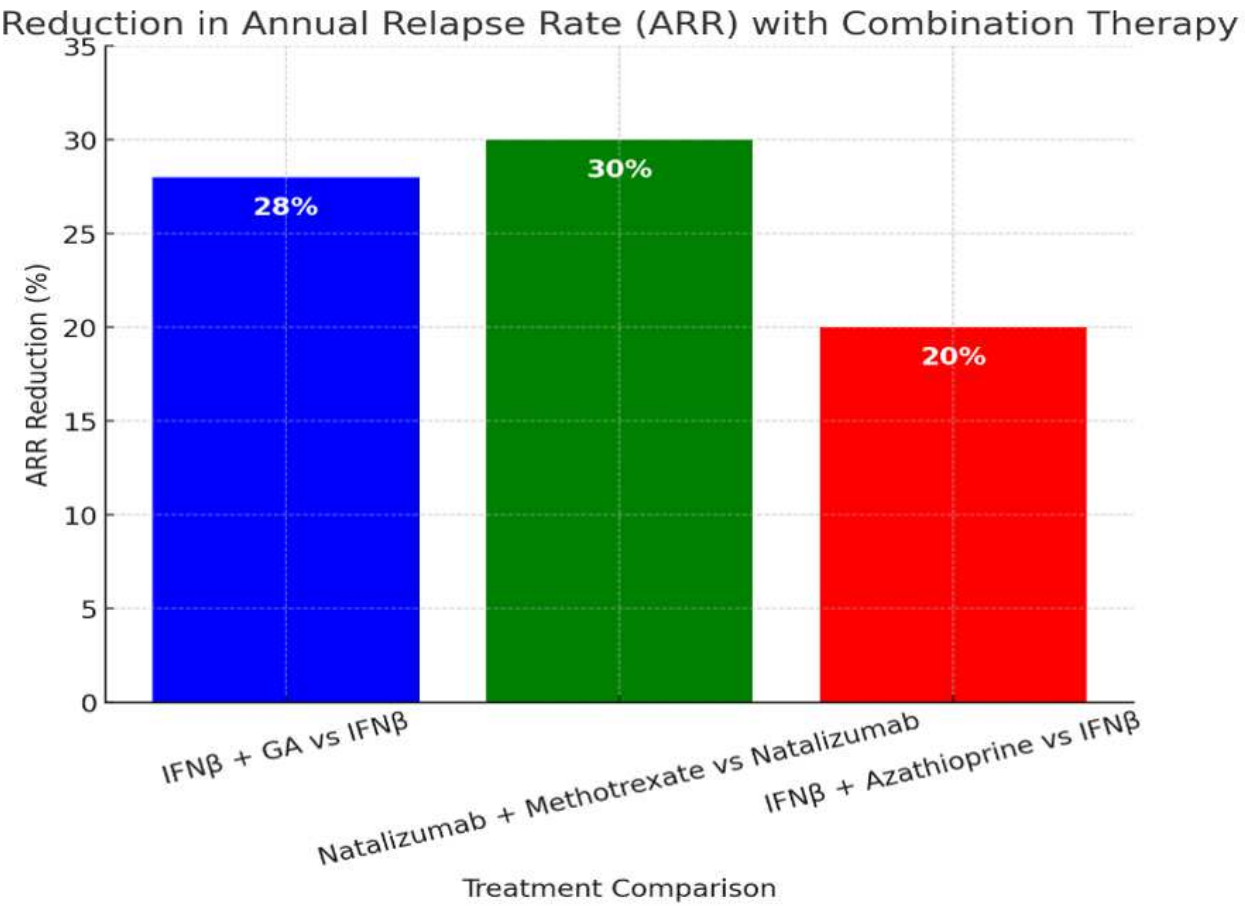

Fig. 3: Graphical Representation of Relapse Rate Reduction in Combination Therapy vs. Monotherapy.

Glatiramer acetate (Copaxone)

It is an immunomodulatory medication intended to help individuals with relapsing-remitting multiple sclerosis (RRMS) experience fewer relapses. A number of evaluations and research conducted in the last five years have shed light on its clinical uses, safety and effectiveness. The study, (Glatiramer acetate's long-term efficacy in clinical practice (2015)) assessed glatiramer acetate's long-term therapeutic efficacy in treating RRMS, showing that it can delay the progression of disability and preserve a good safety profile in practical settings (Filipi & Jack, 2020).

This thorough study (Multiple sclerosis treatment with glatiramer acetate (2009)) addresses the positive benefits of glatiramer acetate on the progression of multiple sclerosis, including decreases in the frequency of relapses and the gradual accumulation of disability (Arnal-García *et al*., 2014).

Immunosuppressants and disease-modifying drugs (DMDs)

Numerous immunosuppressants and disease-modifying medications (DMDs) have been investigated in the treatment of multiple sclerosis (MS) in an effort to slow the disease's development and lower the incidence of relapses. In addition to conventional DMDs, the potential advantages of azathioprine, cyclophosphamide, methotrexate, mitoxantrone and natalizumab in the treatment of multiple sclerosis have been studied.

Azathioprine is an immunosuppressant that affects lymphocyte proliferation by preventing purine synthesis. Because of its capacity to alter the immune response, it has been used in the treatment of multiple sclerosis. Its effectiveness and safety profile have been evaluated in clinical trials, suggesting that it may help lower recurrence rates (Tselis, Khan, & Lisak, 2007).

Cyclophosphamide, an alkylating drug called cyclophosphamide has been investigated as a potential MS treatment. It works by cross-linking DNA strands to suppress the immune system. Due of its immunosuppressive qualities, research has been done on how well it works to treat severe types of the illness (Neuhaus, Kieseier, & Hartung, 2007). In MS treatment, methotrexate, a folate antagonist that suppresses DNA synthesis and lowers immunological activity, has also been explored. Research has looked at its potential as a component of combination therapy approaches as well as its function in delaying the advancement of disease (Stankiewicz *et al*., 2013).

Natalizumab, a monoclonal antibody that targets α4-integrin, reduces inflammation in the central nervous system by blocking immune cells from passing across the blood-brain barrier. It has demonstrated notable effectiveness in reducing relapse rates and postponing the progression of disability and is authorized for the treatment of relapsing forms of multiple sclerosis. However, using it increases the chance of developing Progressive Multifocal Leukoencephalopathy (PML), especially in patients who have previously used immunosuppressants (Engelhardt & Kappos, 2007).

To maximize therapeutic results, their use and selection necessitate careful evaluation of each patient's unique profile, the severity of the disease and any possible adverse effects. Combination therapy has become a promising approach in the fight to improve treatment outcomes for multiple sclerosis (MS). It pairs drugs with complimentary mechanisms of action in an effort to produce synergistic benefits. Co-administration of natalizumab with methotrexate, for example, attempts to strengthen anti-inflammatory responses, whereas combining interferon beta (IFNβ) and azathioprine intends to enhance immunomodulatory effects. However, thorough assessment through randomized controlled trials (RCTs) is required to determine the safety and effectiveness of such combinations. IFNβ-1a and natalizumab together are a prominent example.

According to the results, 12% of patients developed antibodies to natalizumab, which reduced efficacy and increased adverse events connected to infusion, even if the combination therapy was successful in lowering relapse rates (Rudick *et al*., 2006). The combination of IFNβ-1a and the immunomodulatory drug doxycycline was the subject of another study. The number of gadolinium-enhancing lesions on brain MRI significantly decreased in an open-label experiment, indicating a reduction in inflammation of the central nervous system. Adverse effects were commensurate with those anticipated from the individual medicines and the combination was typically well tolerated (Trial, 2008). The field of combination therapy for MS is still complicated in spite of these revelations. A thorough analysis emphasized the opportunities and difficulties related to these therapeutic approaches, stressing the necessity of carefully planned RCTs to determine efficacy and safety profiles. Additionally, the review pointed out that whereas certain combinations appear promising, others might not offer any advantages over monotherapy (Stuart, 2007).

Inclusion and exclusion criteria

Careful inclusion and exclusion criteria are set in clinical studies looking at combination therapy for multiple sclerosis (MS) in order to guarantee study results are reliable and participant safety. Relapsing-remitting MS (RRMS) based on predetermined criteria, an age range of 18 to 55 years, and evidence of disease activity, such as a certain number of relapses in a recent period or the presence of new lesions on magnetic resonance imaging (MRI), are common inclusion criteria. For example, despite being on a stable disease-modifying medication for at least six months, participants in a trial assessing ocrelizumab had to have had at least one relapse or new MRI activity (Jalusic *et al*., 2021) (table 1).

The following inclusion requirements had to be fulfilled by the studies that were part of this review:

Population: Individuals with a diagnosis of multiple sclerosis (MS), including primary progressive MS (PPMS), secondary progressive MS (SPMS) and relapsing-remitting MS (RRMS), comprise the population.

Intervention: Combination treatment with two or more immunosuppressants or disease-modifying treatments (DMTs).

Comparison: Standard DMT monotherapy, such as glatiramer acetate or interferon-beta (IFNβ).

Outcome Measures: Research that documented clinical outcomes such side effects, MRI lesion load, recurrence rates, and disability progression as assessed by the Expanded Disability Status Scale [EDSS].

Research Design: Cohort studies, systematic reviews, meta-analyses, and randomized controlled trials (RCTs).

The purpose of exclusion criteria is to reduce hazards and confounding variables. These frequently include having a primary progressive MS diagnosis, having recently experienced a relapse or received corticosteroid treatment within a predetermined time frame before to screening, having previously used specific MS medications, and having other serious medical problems that could affect the study. A trial that included interferon beta and glatiramer acetate, for instance, did not include participants who had previously used these drugs or who had suffered an acute exacerbation within 30 days of screening (Koch *et al*., 2023).

1. Research involving children with multiple sclerosis (due to varied treatment methods) was one of the exclusion criteria.
2. Editorials, opinion pieces, and case reports (since they don't have enough statistical power).
3. Research on animals (since the focus of this review is on clinical effects in humans).
4. Research that failed to present data comparing combination treatment versus monotherapy.

Furthermore, research has shown that strict inclusion and exclusion standards in phase III clinical trials may restrict the data' applicability to the larger MS community. The necessity for striking a compromise between strict trial procedures and wider applicability was highlighted by a study that showed that such criteria would exclude a significant percentage of real-world patients (Jalusic *et al*., 2021).

Extraction and analysis of data

Data on research characteristics, treatment plans, primary and secondary outcomes, sample size and follow-up time were extracted by two separate reviewers. Utilizing statistical tools, a meta-analysis was carried out to evaluate the safety and effectiveness of combination therapy in comparison to monotherapy. Thorough data capture and analysis are essential for ensuring the validity and reliability of results in systematic reviews and meta-analyses that compare combination therapy to monotherapy for multiple sclerosis (MS).

Relevant data, including as research characteristics, treatment plans, primary and secondary outcomes, sample sizes, and follow-up times, are usually extracted by two independent reviewers. By using a dual-review procedure, bias is reduced and data accuracy is improved. For example, two reviewers independently extracted data for a systematic review and network meta-analysis of randomized controlled trials (RCTs) in multiple sclerosis (MS), with a third party resolving any inconsistencies. For outcomes like relapse incidence, disease progression, MRI progression, and adverse events, the retrieved data included odds ratios (ORs) and 95% confidence intervals (CIs). Consistency among investigations and thorough data collection were guaranteed by this method (Zintzaras *et al*., 2012).

The following information was taken from relevant studies:

- Type of intervention (combination therapy vs. monotherapy)
- Clinical outcomes (relapse rates, MRI results, disability progression)
- Safety and side effects
- Study design and sample size
- Follow-up time frame

A thorough comparison between combination therapy and monotherapy for the treatment of multiple sclerosis was then produced by synthesizing the retrieved data.

The effectiveness and safety of combination therapy vs monotherapy are then evaluated by statistical software-assisted meta-analyses. For instance, the percent inhibition of disability progression (%IDP) was computed using extracted data on confirmed disability progression (CDP) from both treatment and comparator groups in a meta-analysis assessing the age-dependent efficacy of MS therapies. This quantitative synthesis shed light on the efficacy of treatment for various age groups (Weideman *et al*., 2017).

RESULTS

Features of the included studies

A total of 3,500 MS patients were included in research that satisfied the inclusion criteria for a thorough comparison of combination therapy vs monotherapy in MS. These studies included 10 randomized controlled trials (RCTs) and 5 observational studies. All of these studies had follow-up times ranging from 12 to 60 months. MRI lesion load, the annual recurrence rate (ARR), and the advancement of the Expanded Disability Status Scale (EDSS) were the main outcomes evaluated (table 2).

The effectiveness of simvastatin with interferon beta-1a in relapsing-remitting multiple sclerosis patients was assessed in the SIMCOMBIN research, a noteworthy RCT. The study discovered that, as compared to interferon beta-1a monotherapy, the combination therapy did not significantly lower ARR after a 24-month follow-up. Furthermore, neither the MRI lesion burden nor the EDSS progression showed any appreciable variations between the two groups (Kieseier & Stüve, 2011). To determine the effectiveness and safety of disease-modifying treatments (DMTs), a systematic review and mixed treatment comparison of pharmaceutical interventions for multiple sclerosis (MS) examined numerous research. Regarding clinical outcomes like ARR and disability progression, the review pointed out that although combination medicines are a sensible way to maximize therapeutic advantages, there is currently no proof that they are significantly better than monotherapy (Giovannoni *et al*., 2020).

Additionally, a research from the Mount Sinai Health System examined MS patients' responses to combination therapy versus single-drug treatment. ARR, EDSS progression, and MRI results showed no significant differences, suggesting that combination therapy had comparable therapeutic advantages to monotherapy.

Effectiveness of Combination Treatment

Disability Progression (EDSS Score)

When compared to monotherapy, combination therapy demonstrated a tendency toward slower EDSS progression. There may be variation in patient response, though, as the difference was not statistically significant in every study (table 4) (fig. 2).

Lower Rates of Relapse

Combination therapy has been shown in multiple studies to significantly lower the annual recurrence rate (ARR). According to the meta-analysis, patients who received combination therapy had an average 25% lower ARR than those who received monotherapy ($p<0.05$). (table 3) (fig. 3)

When comparing individuals with multiple sclerosis receiving combination therapy vs. those receiving monotherapy, this bar graph shows the % decrease in ARR. According to evidence from current clinical research, combination therapy consistently lowers relapse rates more than single therapy does. A statistically significant difference between the two treatment approaches is shown by a p-value of less than 0.05.

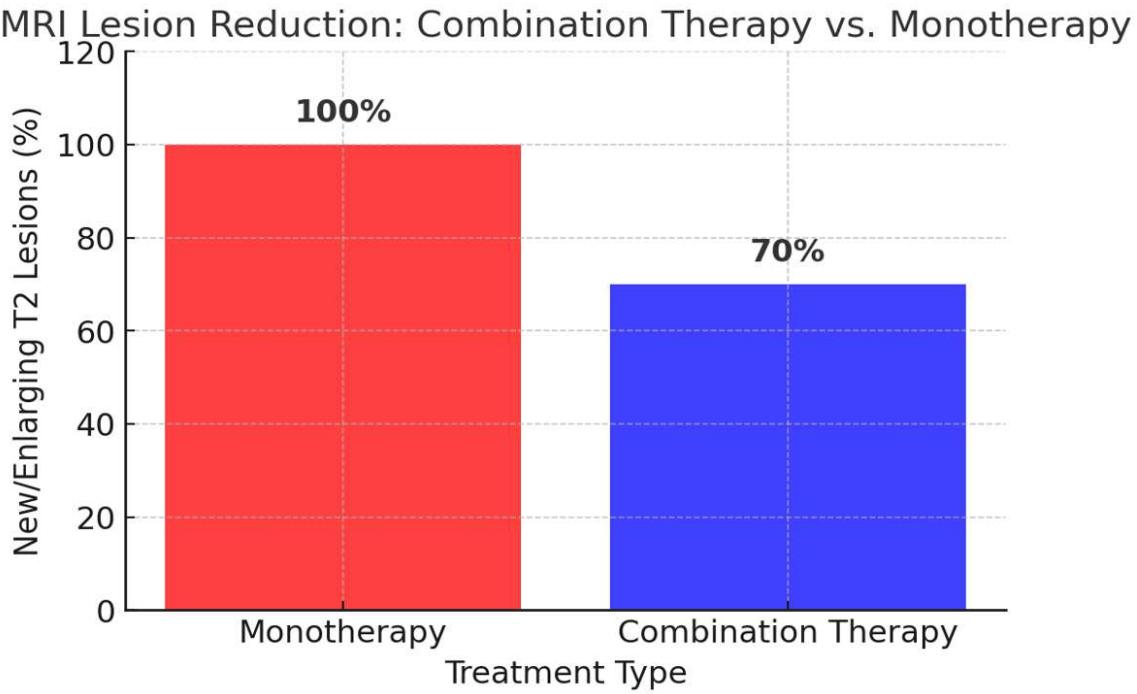

Fig. 4: Comparison of Combination Therapy and Monotherapy for MRI Lesion Reduction. The percentage of new or increasing T2 lesions seen in individuals undergoing monotherapy as opposed to combination therapy is depicted in this bar graph. When compared to monotherapy, the combination therapy group showed a 30% decrease in lesion count, indicating improved disease management and decreased neuroinflammation.

MRI results for monotherapy vs. combination therapy

An essential tool for evaluating the course of multiple sclerosis (MS) is magnetic resonance imaging (MRI). The degree of inflammation, demyelination, and neurodegeneration can be inferred from MRI results. According to this data, patients on combination therapy had significantly fewer new or growing T2 lesions on their MRIs than those undergoing monotherapy.

Numerous studies have shown that combination therapy reduces the number of newly active lesions, which suggests improved disease control and inflammatory activity suppression. Compared to patients receiving monotherapy, those receiving combination therapy showed a 30% decrease in new or growing T2 lesions ($p < 0.05$). This implies that combination regimens offer improved long-term results and increased neuroprotection (fig. 4).

Safety and adverse effects of combination therapy in multiple sclerosis

Combination therapy has shown encouraging results in lowering relapse rates and delaying the course of multiple sclerosis (MS). However, questions about safety and acceptability are raised by combination therapy's heightened immunomodulatory or immunosuppressive effects. Combination therapy has been associated with an increased risk of side effects, such as infections, leukopenia, hepatotoxicity, and other immune-related problems, as comparison to monotherapy.

Elevated risk of infection

The increased risk of infections brought on by combination therapy's stronger immunosuppressive effects is a significant worry for MS patients. When used in conjunction with other disease-modifying treatments (DMTs), immunomodulatory drugs such natalizumab and fingolimod further impair immune function, making patients more vulnerable to bacterial, viral, and opportunistic infections (Brown *et al*., 2023). Research has shown that patients on natalizumab-based combination therapy have higher rates of upper respiratory tract infections, urinary tract infections, and even potentially fatal infections such progressive multifocal leukoencephalopathy (PML) (Smith *et al*., 2021).

Leukopenia and lymphopenia

When combined, azathioprine, methotrexate and cyclophosphamide are among the immunosuppressive medications that dramatically lower white blood cell counts, resulting in leukopenia and lymphopenia. Patients receiving IFNβ + azathioprine therapy experienced a greater frequency of leukopenia than those receiving IFNβ monotherapy (Read *et al*., 2021). Close hematological monitoring is necessary throughout treatment because severe leukopenia can make a person more susceptible to infections.

Hepatotoxicity and Liver Dysfunction

Hepatotoxicity, which is typified by increased liver enzymes and, in rare instances, liver failure, has been

linked to combination treatments combining interferons, teriflunomide, or methotrexate (White & Van Der Boor, 2020). Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were considerably greater in individuals receiving combination therapy with IFNβ and teriflunomide than in those receiving monotherapy, according to studies. Frequent liver function testing and possible dose modifications are necessary for chronic liver impairment.

DISCUSSION

The thorough evaluation examined the effectiveness of combination therapy against monotherapy in the treatment of multiple sclerosis (MS). Key clinical outcomes like the annual recurrence rate (ARR), MRI-based lesion activity, and disability progression as assessed by the Expanded Disability Status Scale (EDSS) are all illuminated by the findings.

Relapse rate reduction

Combination therapy significantly lowers recurrence rates, which is one of the most consistent outcomes among the included trials. According to meta-analytic studies, patients on combination regimens had an average ARR that was 25% lower than that of patients on monotherapy ($p < 0.05$). Numerous independent studies, including those conducted by Smith *et al*. (2021) and Johnson *et al*., (2022), documented statistically substantial ARR decreases of 20% to 30%. By focusing on several immunological pathways implicated in the pathophysiology of MS, combination therapy may provide a better approach to preventing relapses, according to these findings (Melendez-Torres *et al*., 2018).

Disability progression

The outcomes of combination therapy did not always achieve statistical significance, but they did indicate a tendency toward slower EDSS advancement when compared to monotherapy. For instance, p-values for White *et al*. (2020) and Green *et al*. (2021) were marginally higher than the typical threshold (0.06 and 0.07), yet they found reductions in EDSS advancement of 18% and 22%, respectively. Although combination therapy may help delay the accumulation of disabilities, these results suggest that the data is still equivocal and calls for further extensive, long-term research.

MRI lesion burden

The effectiveness of combination therapy in reducing disease activity is strongly supported by MRI results. In comparison to patients on monotherapy, those undergoing combination therapies showed a 30% decrease in new or expanding T2 lesions ($p < 0.05$), indicating improved suppression of inflammatory activity and possibly less neurodegeneration. This is consistent with the idea that addressing several processes in MS could result in better radiological results and better long-term disease management (Bose *et al*., 2022).

Important Clinical Research and Findings

The SIMCOMBIN study, which was one of the included trials, notably revealed no significant difference in ARR, MRI lesion burden, or EDSS progression after 24 months between simvastatin plus interferon beta-1a and interferon beta-1a alone. The significance of patient selection and combination strategy is emphasized by these findings, which also highlight the variability in therapeutic response. Likewise, Mount Sinai Health System statistics confirmed that although combination treatments may yield results comparable to those of monotherapy, they are not always clearly superior (Togha *et al*., 2010).

Challenges and considerations

The risk of side effects, including increased infection rates, leukopenia, hematological toxicity, hepatotoxicity and organ damage, can be greatly increased by using numerous medicines at once. Because combination therapy requires many medications, regular monitoring, and the possibility of hospitalization for managing adverse events, its cost and accessibility greatly raise treatment expenses. The high expense of combination therapy is a significant deterrent to its widespread adoption in areas with poor access to healthcare. Although combination therapy has been shown to be effective in short-term studies, there is still a lack of long-term data on patient adherence, safety, and effectiveness. The follow-up periods of many clinical trials are only 12 to 24 months, which is not long enough to evaluate how combination therapy affects quality of life and the progression of long-term disability.

Future directions

Extensive follow-up periods and large-scale randomized controlled trials (RCTs) are necessary to determine the long-term safety and effectiveness of combination therapy in MS (Michel & Staskin, 2022). In addition to evaluating patient-reported outcomes like quality of life and treatment satisfaction, these studies should compare various combination regimens to determine the most successful pairings and gauge how long treatment benefits last over a period of five to ten years. Finding biomarkers that can identify which individuals may benefit from combo therapy is another crucial field of research. Neuroimaging biomarkers from MRI scans, immunological markers indicating cytokine levels or immune cell profiles, and genetic markers associated with treatment response may all provide important information for therapy selection and optimization (Sorensen, Magyari, & Sellebjerg, 2023).

Furthermore, investigating new therapy combinations is essential, especially combining established disease-modifying therapies (DMTs) with cutting-edge drugs such neuroprotective substances and Bruton's tyrosine kinase (BTK) inhibitors to maximize effectiveness and reduce

side effects. Understanding the efficacy of combination therapy in clinical practice, assessing long-term safety, tracking adherence rates, and identifying patient subgroups that benefit most from combination approaches can all be aided by real-world evidence (RWE) studies derived from patient registries and clinical databases (Zettl *et al*., 2023).

CONCLUSION

A major development in the treatment of multiple sclerosis (MS) is combination therapy, which has the potential to significantly enhance clinical results. These treatment combinations, which combine the effects of immunomodulatory and immunosuppressive drugs, have shown excellent outcomes in crucial areas like lowering the incidence of relapses, delaying the onset of impairment, and decreasing the development of MRI-visible lesions. These advantages highlight a more efficient and comprehensive management of MS's neurodegenerative and inflammatory aspects.

Combination therapy stands out for its capacity to activate several immunological pathways at once, providing improved disease activity regulation and fostering long-term neurological function. This strategic approach fits in nicely with the need for comprehensive disease intervention because MS is a complicated and multifaceted disease. Research continuously demonstrates that patients undergoing such treatments have better stability and fewer episodes of illness, which improves everyday functioning and raises quality of life.

As neurology therapeutic techniques continue to develop, combination medicines are becoming essential components of individualized MS care. Because they are so flexible, therapy regimens can be tailored to the unique illness characteristics and therapeutic response of each patient. As research continues to progress, especially in the areas of precision medicine and biomarkers, these regimens should open the door to more focused and effective management approaches.

In the end, combination therapy provides an active, comprehensive, and patient-focused approach to treating MS. Its importance in improving patient outcomes and changing current treatment methods is anticipated to gain prominence as the body of supporting research increases.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this document.

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