Nicholas Adlard | nicholas.adlard@novartis.com

CO78

High-Efficacy Therapies (HETs) First versus an Escalation Approach in Multiple Sclerosis: A Targeted Literature Review

Salman Hussain[1], Mohit Kumar Bhutani[1], Santosh Tiwari[1], Preety Rajora[1], Sheshank Madiraju[1], Olwyn Grennan[2], Roisin Brennan[2], Nicholas Adlard[3]

[1]Novartis Healthcare Private Limited, Hyderabad, Telangana, India; [2]Novartis Ireland Limited, Dublin, Ireland; [3]Novartis Pharma AG, Basel, Switzerland

KEY FINDINGS & CONCLUSIONS

- This TLR indicates that initiating HETs as a primary treatment for MS leads to better therapeutic outcomes, including fewer relapses, more patients reaching NEDA, and slower progression of disability compared to an escalation approach. Overall, evidence supports HETs as a preferred option for MS treatment.

This study is sponsored by Novartis Pharma AG, Basel, Switzerland

Poster presented at the ISPOR-Europe 2024, 17–20th November 2024, Barcelona, Spain

INTRODUCTION

- Multiple sclerosis (MS) is a multifaceted chronic disease characterised by inflammation, neurodegeneration, and progression.
- There are over 20 disease-modifying therapies (DMTs) available for the management of MS.
- MS disease management include two treatment paradigms: the escalation approach, where patients switch from low or moderate-efficacy DMTs to high-efficacy therapies (HETs) based on clinical assessment, or the alternative approach of initiating HETs as the first line of treatment.

OBJECTIVE

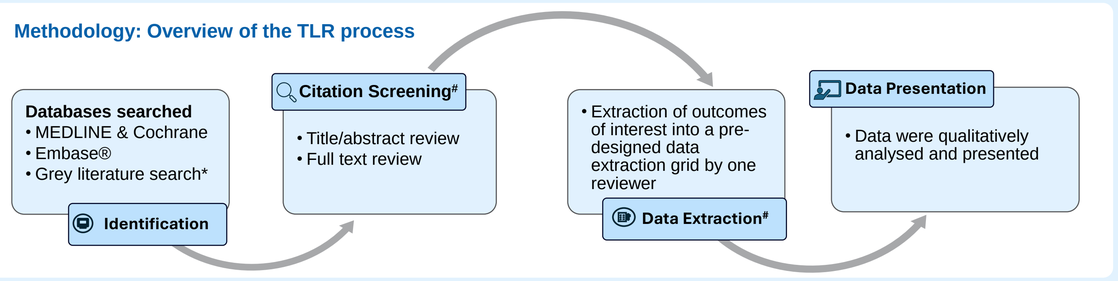
- The objective of this targeted literature review (TLR) was to identify and summarise evidence on the benefits of HETs first vs. escalation approach in patients with MS.

METHODS

Studies meeting the following criteria were eligible for inclusion in the review:

- Studies including people living with multiple sclerosis (plwMS) receiving HETs first or escalation to HETs and published between 2016 and 2023.
- Studies reporting clinical benefits on below outcomes:
  - Relapse, Disability, NEDA, Cognition, MRI lesion, Brain volume, and Disease transition

Methodology: Overview of the TLR process

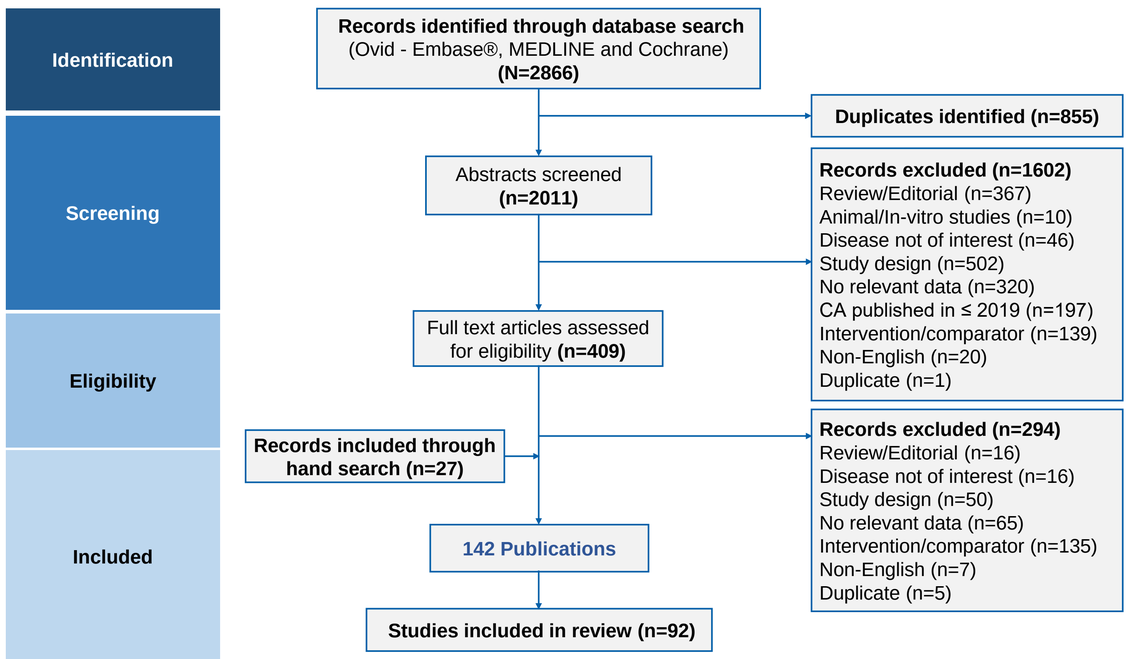


*Includes manual searches
#Literature screening and data extraction were performed by one reviewer and random checked by another reviewer

RESULTS

- Overall, 92 unique studies were included in the review. Of these, 66 assessed HETs first, while 53 studies focused on the escalation to HETs.
- The study selection process is presented in the PRISMA flowchart (**Figure 1**).

Figure 1. PRISMA flowchart showing study selection process



Abbreviations: CA: Conference Abstract; Embase: Excerpta Medica Database; MEDLINE: Medical Literature Analysis and Retrieval System Online; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Included study design characteristics

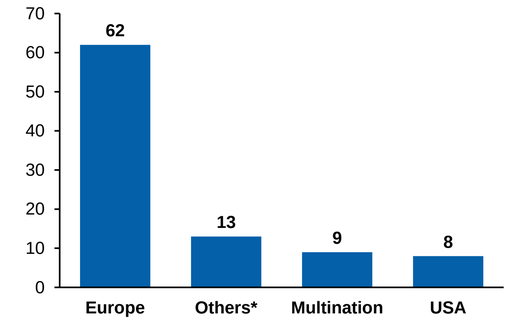
- Majority of the included studies were conducted in real-world setting and were conducted in the European region (**Figure 2**).
- Most of the studies included were of a comparative nature
  - HETs first vs. escalation to HETs (n=20)
  - HETs first vs. other DMTs (n=24)
  - Escalation to HETs vs. no escalation (n=12)
  - HETs first / escalation to HETs only (n=36)
- The list of DMTs reported by HETs first / HETs escalation studies are enlisted in **Table 1**.

Table 1. List of high-efficacy and low-moderate efficacy DMTs as reported by authors

List of high-efficacy DMTs	List of low-moderate efficacy DMTs
Alemtuzumab, Natalizumab	Interferon beta-1a
Ofatumumab, Ocrelizumab	Interferon beta-1b
Rituximab	Glatiramer acetate
Siponimod, Ozanimod, Ponesimod	Teriflunomide
Mitoxantrone	Dimethyl fumarate
Cyclophosphamide	Azathioprine
Fingolimod*	Fingolimod*
Cladribine*	Cladribine*

*Assessed/reported as both high-efficacy and low-moderate efficacy DMTs among the included studies

Figure 2. Geographic distribution of included studies



*Includes Argentina; Australia; Canada; Colombia; India; Kuwait; Mexico; Thailand

- Among the 66 studies investigating HETs first, a majority of studies highlighted the benefits of HETs first in comparison to escalating to HETs or using first-line DMTs (low-moderate efficacy DMTs). These findings consistently highlighted lower relapse rates, reduced disability progression, attainment of no evidence of disease activity (NEDA), and a marked decrease in the presence of active MRI lesions.
- Similarly, most of the studies evaluating escalation approach emphasized on the benefits of escalating to HETs compared to not escalating to HETs (continuing low-moderate efficacy DMTs). These outcomes encompassed lower relapse rates, decelerated disability progression, attainment of NEDA, reductions in active MRI lesions, and a slower rate of brain volume loss.
- Twenty head-to-head studies comparing the use of HETs first with escalation strategy were assessed to gain deeper insights.

Head-to-head comparisons

- A total of 20 studies involving 15,772 patients compared the use of HETs with an escalation approach **(Table 2).**
- Mean (SD) age of the patients across studies lied in the range of 30 (9.3) years to 48.6 (10.8) years.
- Patients in HETs first group were younger, had shorter disease duration, and high disease activity compared to patients in escalation group.
- Most studies (75%) indicated that starting HETs is more beneficial than escalating treatment, as it leads to lower relapse rates, reduced disability progression, improved cognition, fewer MRI lesions, and achieving NEDA **(Table 2).**

Table 2. Head-to-head studies comparing HET first vs. escalation approach: Summary of findings

Primary Study	Population	N	HETs compared to escalation (core findings)
Favoured HETs first compared to escalation			
Arnett et al. 2023[1]; (abstract)	MS	582	**Relapse:** Patients who initiated HETs first had significantly lower relapse rate compared to escalation (HR=0.47; *p*=0.001).
Alonso et al. 2023[2]; (full-text)	RRMS	323	**Relapse:** Lower proportion of patients with relapse were observed in HETs first compared to escalation (50.0% vs. 73.0%) with an OR of 0.55 (95% CI: 0.22–0.76). **NEDA:** The superior effect of patients receiving HETs first vs. patients with escalation on NEDA-3 was highly significant at both Year 1 (85.8% vs. 62.5%; *p*=0.02) and at Year 2 (83.2% vs. 70.4%; *p*<0.01) with an adjusted OR of 5.58 (95% CI: 2.08–16.29; *p*<0.01).
Biernacki et al. 2022[3]; (full-text)	RRMS	570	**Relapse:** HET first (fingolimod) has proven to be highly efficacious in reducing ARR from the first year to five year (0.10–0.00) compared to escalation to fingolimod (0.15–0.06). **Disability progression:** Compared to baseline, only patients who received HET first (fingolimod) had lower EDSS score at study end. HET first group had the highest ratio of patients free of confirmed disability worsening (*p*=0.033) at any point in the study.
Cannizzaro et al 2020[4]; (abstract)	RRMS	543	**NEDA:** Patients treated with HET first (fingolimod) had a higher probability of being NEDA after 2 years compared to escalation (62.1% vs. 47.4%).
Cerqueira et al. 2022[5]; (abstract)	RMS	756	**NEDA**: Patients initiating OCR as HET first had favourable outcomes for NEDA over 7 years of treatment compared to escalation (IFN–OCR switchers). **Disability progression:** Patients who received OCR as HET first showed sustained benefits to 24Week-CDP outcomes compared to (IFN–OCR switchers).
Davidescu et al. 2022[6]; (full-text)	RRMS	51	**Relapse and Disability progression:** Patients who initiated natalizumab as HET first had a mild reduction in the EDSS value of 0.16, which was statistically non-significant (p=0.52) in comparison to those who were escalated to Natalizumab, in whom there was observed an increase in the EDSS value of 0.21, also statistically non-significant (*p*=0.41).
Geiger et al. 2022[7]; (full-text)	MS	694	**Relapse:** Patients in the HETs first cohort had a significantly lower annualised rate of events often associated with a relapse compared to the escalation cohort (0.37 vs. 0.56). **Safety:** Patients in the HETs first cohort had a significantly fewer hospitalisations and non-DMT outpatient visits compared to the escalation cohort.
Guger et al. 2023[8]; (abstract)	RRMS	773	**Relapse:** Mean ARR were lower in patients received HETs first (0.12) compared to escalation (0.39). A decreased relapse probability of 74% was found in patients received HETs first compared to escalation (IRR=0.26; 95% CI: 0.20–0.35; p<0.001). Analysing the time to the first relapse by Cox regression indicated an increased risk of 83% for the escalation (HR: 0.17; 95% CI: 0.12–0.25; *p*<0.001). **Disability progression:** An increased probability of sustained EDSS progression for 12 weeks was observed for the escalation cohort(51%) compared to HETs first with a HR of 0.49 (95% CI: 0.29–0.82); *p*=0.008).
Harding et al. 2019[9]; (full-text)	MS	592	**Disability progression:** Mean (SD) 5-year change in EDSS score was lower in the HETs first group than the escalation group (0.3 [1.5] vs. 1.2 [1.5]); this remained significant after adjustment for relevant covariates (β =−0.85; 95% CI: −1.38−0.32; *p*=0.002). Median (95% CI) time to sustained accumulation of disability was 6.0 (3.17–9.16) years for HETs first and 3.14 (2.77–4.00) years for escalation (*p*=0.05).
Iaffaldano et al. 2021[10]; (full-text)	RRMS	726	**Disability progression:** The estimated mean (95% CI) baseline EDSS was 2.45 (2.26–2.64) in the HETs first group and 2.52 (2.33–2.71) in the escalation group. The EDSS score increased in both groups however, score increment was higher in the escalation cohort. The estimated mean delta-EDSS differences vs. baseline between the two groups tended to increase from 0.1 (0.01–0.19; *p*= 0.03) at 1 year, to 0.30 (0.07–0.53, *p*=0.009) and to 0.64 (0.35–0.93; *p*<0.001) at 5 and 8 years respectively, while at 10 years (the last year of study observation) it was 0.67 (0.31–1.03; *p*=0.0003).
Labiano-Fontcuberta et al. 2022[11]; (full-text)	MS	695	**Cognition:** The HETs first group had a lower proportion of cognitively declining patients compared to the escalation group, with significant differences noted in the Raw PST score criteria. Specifically, only 6.3% of patients in the HETs first group were cognitively impaired, compared to 16.7% in the escalation group (*p*=0.021).
Negrotto et al. 2022[12]; (full-text)	RRMS	269	**Relapse:** Relapse were less frequently reported in patients initiated on HET first (cladribine: 12.5%; 5/32) compared to escalation (87.5%; 27/32).
Prosperini et al. 2020[13]; (full-text)	RRMS	813	**Disability progression:** In a propensity score matched sample, a lower proportion of patients in the HET first group reached the disability milestone of an EDSS score of ≥6.0 compared to the escalation group, with rates of 28.0% and 38.7%, respectively. **Safety:** Serious adverse events occurred more frequently after HETs first (8/75; 10.7%) than escalation (18/738; 2.4%) (OR=3.36; *p*=0.015).
Rojas et al. 2022[14]; (full-text)	RRMS	431	**Relapse:** Patients who received HETs first had a significantly higher rate of being relapse-free compared to those who underwent escalation (60.0% vs. 25.0%). Additionally, initiating HETs first notably reduced the risk of new relapse during follow-up (aHR=0.66; 95% CI: 0.49–0.89; *p*=0.006). **Disability progression:** Patients who received HETs first showed a significantly higher rate of being free from EDSS progression compared to those who underwent escalation (80.0% vs. 53.0%). Additionally, HETs first reduced the risk of EDSS progression during follow-up (aHR=0.62; 95% CI: 0.40–0.98; *p*=0.04). **NEDA:** Patients who initiated HETs first had a significantly higher rate of reaching NEDA compared to those who underwent escalation (45.0% vs. 19.0%), and HETs first also lowered the risk of any disease activity during follow-up (aHR=0.64; 95% CI: 0.48–0.86; *p*=0.003). **MRI lesion risk**: Patients who received HETs first showed a significantly higher proportion of being free from new MRI lesions compared to those who underwent escalation (50.0% vs. 22.0%). Additionally, HETs first reduced the risk of relapse during follow-up (aHR=0.55; 95% CI: 0.40–0.75; *p*<0.001).
Spelman et al. 2021[15]; (full-text)	CIS or RRMS	4861	**Relapse:** Patient who received HETs first experienced a significantly greater reduction in the rate of first relapse compared to escalation (aHR=0.24; 95% CI: 0.19–0.30). **Disability progression:** Patients who received HETs first were associated with a slightly larger reduction in the rate of confirmed disability worsening when compared to the escalation approach (HR=0.68; 95% CI: 0.61–0.76). **Safety:** A higher percentage of patients in the escalation strategy discontinued their index DMT due to lack of effectiveness/disease activity/progression (37.4%) compared to those in the HET strategy (30.7%).
Similar effects of starting with HETs or escalation to HETs approach			
Arena et al. 2023[16]; (full-text)	RRMS	217	**Relapse:** A higher percentage of patients experienced no clinical relapse after 2 years with HET first (cladribine) compared with escalation (80.3% vs. 76.5%). **Disability progression:** At two years, a higher percentage of patients in the HET first (cladribine) group experienced no EDSS progression compared to those in the escalation group (92.3% vs. 83.9%). **NEDA:** At two years, a higher percentage of patients achieved NEDA in the HET first (cladribine) group compared to the escalation group (35.9% vs. 35.0%). **MRI activity:** At two years, MRI activity was found to be comparable in the HET first (cladribine) group compared to the escalation (51.6% vs. 42.0%). **Safety:** A lower rate of adverse events were observed in patients who initiated HETs first (cladribine) compared to escalation approach (70.8% vs. 41.2%).
Gauer et al. 2023[17]; (full-text)	RRMS	1227	**Relapse:** Relapse risk was lower in escalation group (escalated to fingolimod) compared to HETs first group. Mean 5-year ARR in escalation group was 0.24 (95% CI: 0.21–0.27) and in the HETs first group was 0.30 (95% CI: 0.19–0.41). **Safety:** A lower percentage of patients in the escalation group discontinued treatment due to inefficacy compared to those in the HETs first group (41.0% vs. 62.0%), while the opposite was true for intolerance (29.0% vs. 13.0%).
Hunter et al. 2020[18]; (full-text)	RRMS	875	**Relapse:** The effects of HETs first (fingolimod) were similar to those observed with escalation approach.
Portaccio et al. 2022[19]; (full-text)	PPMS	409	**Disability progression:** Both the first and escalation approaches of HETs demonstrated a protective effect in the risk of reaching an EDSS score of 7.0, with aHR of 0.31 and 0.32, respectively, in a propensity score matched group.
Torgauten et al. 2021[20]; (full-text)	MS	365	**Relapse:** ARR was comparable in HET first (rituximab) group compared to escalation to HET group (0.02 vs. 0.03).

Abbreviations: aHR: Adjusted hazard ratio; ARR: Annualised relapse rate; CDP: Confirmed disability progression; DMTs: Disease-modifying therapies; EDSS: Expanded disability status scale; HETs: High-efficacy therapies; HR: Hazard ratio; IFN: Interferon; IRR: Incidence rate ratio; MS: Multiple sclerosis; NEDA: No evidence of disease activity; OCR: Ocrelizumab; OR: Odds ratio; PST: Positive symptom total; RRMS: Relapsing-remitting multiple sclerosis; SPMS: Secondary progressive multiple sclerosis

References

1. Arnett S, et al. Mult Scler J. 2023;29(3 Suppl): 613.
2. Alonso R, et al. Mult Scler J Exp Transl Clin. 2023;9(1)
3. Biernacki T, et al. PLoS ONE. 2022;17(4):e0267346
4. Cannizzaro M, et al. Mult Scler J. 2020;26(3 Suppl):523–524
5. Cerqueira J, et al. Mult Scler J. 2022;28(3 Suppl): 634
6. Davidescu E, et al. CNS Neurol Disord Drug Targets. 2022;21:326–334
7. Geiger C, et al. Neurol Ther. 2023;12:1709–1728
8. Guger M, et al. Mult Scler J. 2023;29(3 Suppl):1012–1013
9. Harding K, et al. JAMA Neurol. 2019;76(5):536–541
10. Iaffaldano P, et al. Ther Adv Neurol Disord. 2021;14
11. Labiano-Fontcuberta A, et al. Mult Scler Rela Disord. 2022;64
12. Negrotto L, et al. Mult Scler Relat Disord. 2022;68
13. Prosperini L, et al. Neurotherapeutics. 2020;17(3): 994–1004
14. Rojas J, et al. Clin Neuropharm. 2022;45:45–51
15. Spelman T, et al. JAMA Neurol. 2021:E1–E8
16. Arena S, et al. Curr Neuropharmacol. 2023;22
17. Gauer L, et al. Rev Neurol. 2023;S0035
18. Hunter S, et al. Mult Scler Relat Disord. 2020;45:102346
19. Portaccio E, et al. JAMA Neurol. 2022;79(9):869-878
20. Torgauten H, et al. Mult Scler J Exp Transl Clin. 2021:7(1)

Disclosures

Salman Hussain, Mohit Kumar Bhutani, Sheshank Madiraju, Olwyn Grennan, Roisin Brennan, and Nicholas Adlard are employees of Novartis. Santosh Tiwari, and Preety Rajora were employees of Novartis at the time of study.

Scan to obtain:

- Poster
- Plain language summary
- Slides
- Supplementary material

https://www.medicalcongressposters.com//Default.aspx?doc=ed919