Discontinuation of High-Efficacy Disease-Modifying Therapies in Multiple Sclerosis

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BACKGROUND

- Multiple Sclerosis (MS) is an autoimmune-mediated neurological disorder that causes central nervous system damage leading to neurological deficits[1,2]
- 1 million individuals in the United States are living with MS, a majority are female and between 20-50 years old at diagnosis[3]
- Disease-modifying therapies (DMTs) are treatments that have been shown to reduce the activity and progression of MS. High-efficacy DMTs are those that have been found to reduce relapses by more than 50% on average[4]
- Assessment of recent studies focused on the rates and reasons for discontinuation of high-efficacy DMTs is needed to inform clinical decision-making

OBJECTIVE

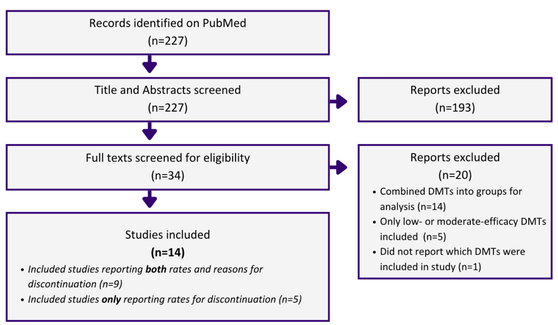
Identify the rates and reasons for discontinuation of high-efficacy DMTs among adult patients with MS

METHODS

Key inclusion criteria for this targeted literature review:

- Observational studies published in English between January 2020 and April 2024
- Adult patients with Multiple Sclerosis
- High-efficacy Disease-Modifying Therapies (DMTs):
  - Alemtuzumab (Lemtrada)
  - Cladribine (Mavenclad)
  - Mitoxantrone (Novantrone)
  - Natalizumab (Tysabri)
  - Ocrelizumab (Ocrevus)
  - Ofatumumab (Kesimpta)
  - Ublituximab (Briumvi)
- Rates and/or reasons for discontinuation or persistence of high-efficacy DMTs

Figure 1. PRISMA Flow Diagram



RESULTS

Table 1. Study Characteristics

Study (Author, Year)	Country	Study Design	Data Source	Sample Size	Age	Sex (Percent Female)	Type of MS (Percent RRMS)	High Efficacy DMTs Included
Bose, 2021[5]	Canada	Retrospective observational	EHR [*Ottowa Hospital MS Clinic*]	Alemtuzumab: N=46 Cladribine: N=65	Median: Alemtuzumab: 36.1 (IQR: 31-42) Cladribine: 43.8 (IQR: 37-50)	Alemtuzumab: 82.6% Cladribine: 70.8%	Alemtuzumab: 93.5% Cladribine: 53.8%	Alemtuzumab Cladribine
Brownlee, 2023[6]	England	Retrospective observational	Claims Database [*Blueteq® High-Cost Drug Platform*]	Cladribine: N=1934	Not reported	Not reported	Not reported	Cladribine
Coban, 2021[2]	USA	Retrospective observational	EHR [*University of Connecticut Health MS Center*]	Ocrelizumab: N=82	Mean: 41 ± 11	RRMS: 55% PPMS: 21% SPMS: 66%	72%	Ocrelizumab
Engmann, 2021[1]	USA	Retrospective observational	Claims Database [*IQVIA PharMetrics Plus Commercial Claims®*]	Natalizumab: N=341 Ocrelizumab: N=1319	Mean: Natalizumab: 41.3 ± 11 Ocrelizumab: 47.9 ± 9.9	Natalizumab: 72.4% Ocrelizumab: 65.7%	Not reported	Natalizumab Ocrelizumab
Gorritz, 2023[7]	USA	Retrospective observational	Claims Database [*IQVIA PharMetrics Plus Commercial Claims®*]	Ofatumumab: N=576	Mean: 46.7	79.4%	Not reported	Ofatumumab
Horakova, 2020[8]	Czechia	Retrospective observational	EHR [*General University Hospital in Prague*]	Natalizumab: N=193	Mean: 34.9 ± 8.84	71.5%	100%	Natalizumab
Moccia, 2022[9]	Italy	Retrospective observational	EHR [*Campania Region Hospital Centers*]	Alemtuzumab: N=31 Cladribine: N=30 Natalizumab: N=261 Ocrelizumab: N=398	Mean: Alemtuzumab: 35.4 ± 8.3 Cladribine: 43.1 ± 12.0 Natalizumab: 34.1 ± 11.0 Ocrelizumab: 45.7 ± 11.0	Alemtuzumab: 67% Cladribine: 73% Natalizumab: 70% Ocrelizumab: 56%	Not reported	Alemtuzumab Cladribine Natalizumab Ocrelizumab
Okuda, 2022[10]	USA	Retrospective observational	EHR [*Multiple Sclerosis and Neuroimmunology Clinic at The University of Texas Southwestern Medical Center*]	Alemtuzumab: N=29 Natalizumab: N=167 Ocrelizumab: N=133	Mean at diagnosis: 38.6 ± 9.9	85.7%	Not reported	Alemtuzumab Natalizumab Ocrelizumab
Pardo, 2022[11]	USA	Retrospective observational	Claims Database [*MarketScan® Commercial and Medicare Supplemental*]	Natalizumab: N=120 Ocrelizumab: N=524	Mean: Natalizumab: 43 ± 11 Ocrelizumab: 49 ± 10	Natalizumab: 79% Ocrelizumab: 67%	Not reported	Natalizumab Ocrelizumab
Rauma, 2022[12]	Finland	Prospective and retrospective observational	Registry [*Finnish MS Registry*]	Cladribine: N=179	Mean at initiation: 35.9 ± 9.9	85.5%	98.9%	Cladribine
Santos, 2023[13]	Portugal	Retrospective observational	EHR [*Portuguese Tertiary Hospitals*]	Cladribine: N=182	Mean at initiation: 41.1 ± 12.1	68.7%	88.5%	Cladribine
Sorensen, 2023[14]	Denmark	Retrospective observational	Registry [*The Danish Multiple Sclerosis Registry*]	Cladribine: N=268	Mean: 40.6 ± 10.7	66.8%	97.8%	Cladribine
Spelman, 2023[15]	Global	Retrospective observational	Registry [*MSBase Registry*]	Cladribine: N=633	Mean: 44.1 ± 12.3	76.2%	87.1%	Cladribine
Zhu, 2023[16]	Global	Retrospective observational	Registry [*MSBase Registry*]	Ocrelizumab: N=425	Mean: 42.8 ± 11.2	72%	100%	Cladribine

Abbreviations: MS – Multiple Sclerosis, EHR - Electronic Health Record, RRMS – Relapsing-Remitting Multiple Sclerosis, PPMS – Primary Progressive Multiple Sclerosis, SPMS – Secondary Progressive Multiple Sclerosis, DMT – Disease-Modifying Therapy

Table 2. Summary of Discontinuation Rates and Follow-Up Period Ranges

DMT	Follow-Up Ranges in months	Rate Ranges Across All Follow-Up Time	Rates After 12-24 months of Follow-Up
Alemtuzumab	13.8-38.4	0.4-54.8%	54.8%
Cladribine	11.8-39.6	0.0-21.5%	4.3-11.3%
Natalizumab	12-54	34.4-77.8%	34.4-45.0%
Ocrelizumab	12-34.8	1.0-25.0%	1.0-25.0%
Ofatumumab	6-12	19.3-25.5%	25.5%

Legend Explanation for Figures 3 and 4:

Intolerability[10]: adverse drug reactions like injection site reaction, hair thinning, GI side effects, headache, flushing
Medical Reasons[10]: lab abnormalities, anti-JC virus antibody positive with high index values, presence of clinical relapses, disability progression, development of new/enlarging T2 lesions on MRI of CNS
Non-medical Reasons[10]: family planning, desire for oral treatment, insurance coverage, costs, desire to decrease medication burden, preference to switch, subjective report of lack of efficacy

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Conflict of Interest: DV has done consulting with Genentech.

References: 1. Engmann NJ.2021. Journal of Managed Care & Specialty Pharmacy. PMID: 33624535 2. Coban H, 2021. Multiple Sclerosis and Related Disorders. PMID: 34077828 3. Samjoo IA. 2021. Journal of Comparative Effectiveness Research. PMID: 33620251. 4. National Multiple Sclerosis Society [Internet]. Who Gets MS? Available from: https://www.nationalmssociety.org/What-is-MS/Who-Gets-MS 5. Bose G. 2021. Multiple Sclerosis and Related Disorders. PMID:33901969. 6. Brownlee, W. 2023. Multiple Sclerosis and Related Disorders. PMID: 37639781. 7. Gorritz, M. 2023. CMSC Annual Meeting. 8. Horakova D. 2020. Multiple Sclerosis and Related Disorders. PMID: 33296966 9. Moccia M. 2022. Journal of Neurology. PMID: 35953597. 10. Okuda, D.T. 2022. Multiple Sclerosis and Related Disorders. PMID: 35661567. 11. Pardo, G. 2022. Neurology and Therapy. PMID: 35020156 12. Rauma I. 2022. Multiple Sclerosis and Related Disorders. PMID: 35483129. 13. Santos M. 2023. Clinical Neuropharmacology. PMID: 37191564. 14. Sorensen PS. 2023. Multiple Sclerosis and Related Disorders. PMID: 36623393. 15. Spelman T. 2023. Multiple Sclerosis. PMID: 36433775. 16. Zhu C. 2023. JAMA Neurology. PMID: 37273217.

Summary of Results:

- We identified 14 studies investigating the rates and/or reasons for discontinuation of high-efficacy DMTs
  - 9 studies reported both rates and reasons
  - 5 studies reported only rates
- Studies varied widely with:
  - Sample sizes between 29-1,934 participants per DMT
  - Follow-up spanning 11.8-54 months with most in the range of 12-24 months
  - Differing discontinuation definitions
- Alemtuzumab, cladribine, and natalizumab were primarily discontinued due to **medical reasons**
- Ocrelizumab was primarily discontinued due to **intolerability**
- Ofatumumab did have discontinuation reasons reported

Figure 3. Discontinuation Rates and Reasons of High-Efficacy DMTs

Follow-up periods are listed next to each study in months.
Brownlee, Engmann, Gorritz, Moccia, and Pardo studies were not included in Figures 3 or 4, because reasons for discontinuation were not reported.

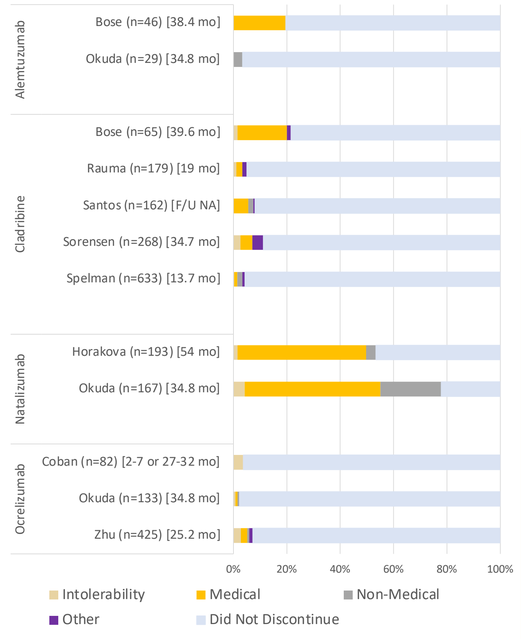
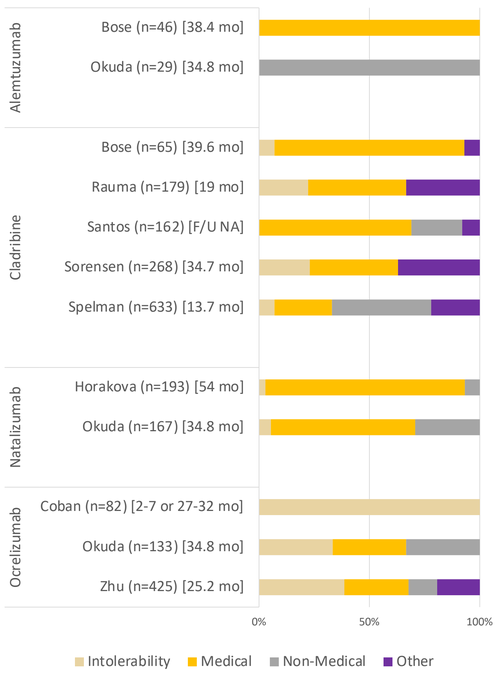


Figure 4. Reasons for Discontinuation of High-Efficacy DMTs by Study

Follow-up periods are listed next to each study in months.



CONCLUSIONS & IMPLICATIONS:

- Alemtuzumab and natalizumab had the highest rates of discontinuation after 12-24 months and were discontinued primarily for medical reasons
- **Treatment efficacy was the driving factor in the discontinuation of high-efficacy DMTs compared to intolerability or non-medical reasons after 12-24 months**
- Future studies should continue to explore discontinuation trends among newer high-efficacy DMTs, including ofatumumab and ublituximab, and utilize a consistent definition for DMT discontinuation