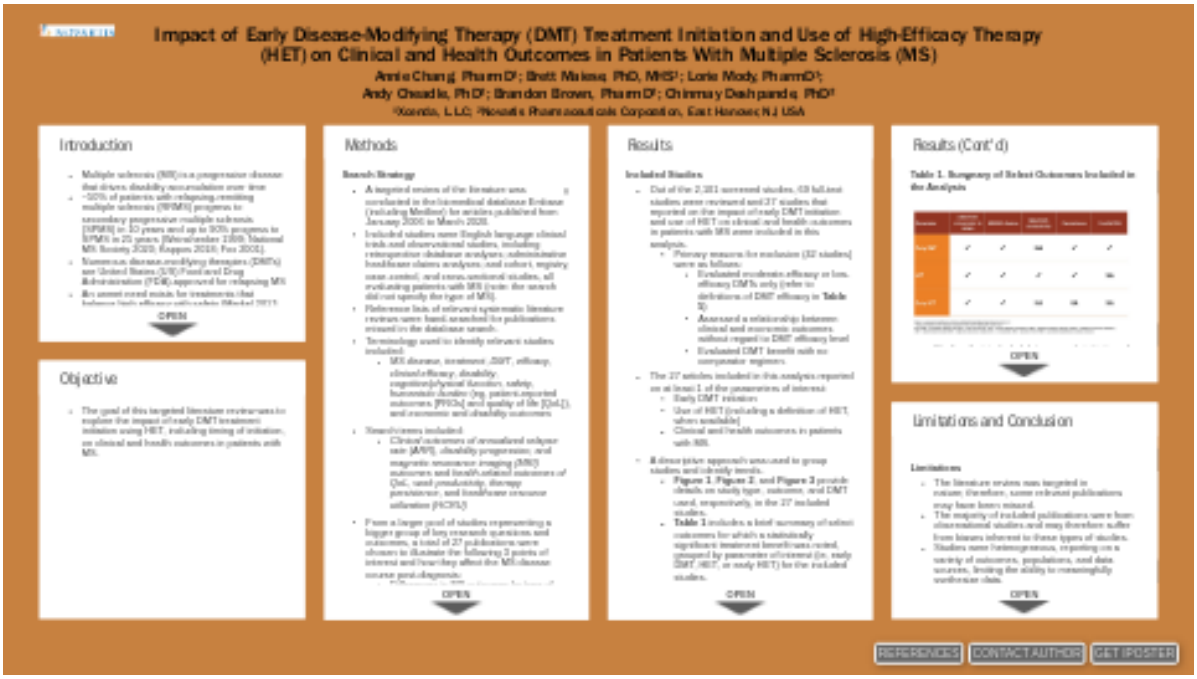
Impact of Early Disease-Modifying Therapy (DMT) Treatment Initiation and Use of High-Efficacy Therapy (HET) on Clinical and Health Outcomes in Patients With Multiple Sclerosis (MS)



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INTRODUCTION

- Multiple sclerosis (MS) is a progressive disease that drives disability accumulation over time
- ~50% of patients with relapsing-remitting multiple sclerosis (RRMS) progress to secondary progressive multiple sclerosis (SPMS) in 10 years and up to 90% progress to SPMS in 25 years (Weinshenker 1999; National MS Society 2020; Kappos 2018; Fox 2001).
- Numerous disease-modifying therapies (DMTs) are United States (US) Food and Drug Administration (FDA)-approved for relapsing MS
- An unmet need exists for treatments that balance high efficacy with safety (Merkel 2017; Harding 2019; Tice 2017)
- Uncertainty exists around optimal timing of initiation of therapy with high-efficacy DMTs (ie, when in a patient's disease course)
- Further need exists to understand benefits of early use of high-efficacy therapy (HET) vs starting with lower-efficacy therapy and escalating to high efficacy if disease worsens (Stankiewicz 2019; Weideman 2017).

OBJECTIVE

- The goal of this targeted literature review was to explore the impact of early DMT treatment initiation using HET, including timing of initiation, on clinical and health outcomes in patients with MS.

METHODS

Search Strategy

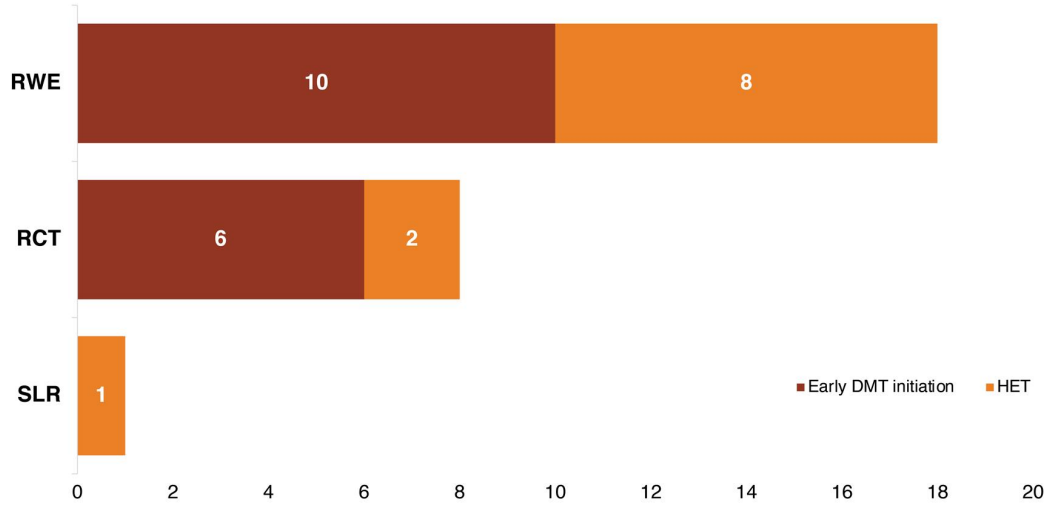
- A targeted review of the literature was conducted in the biomedical database Embase® (including Medline) for articles published from January 2006 to March 2020.
- Included studies were English language clinical trials and observational studies, including retrospective database analyses; administrative healthcare claims analyses; and cohort, registry, case-control, and cross-sectional studies, all evaluating patients with MS (note: the search did not specify the type of MS).
- Reference lists of relevant systematic literature reviews were hand-searched for publications missed in the database search.
- Terminology used to identify relevant studies included:
  - *MS disease*, *treatment*, *DMT*, *efficacy*, *clinical efficacy*, *disability*, *cognitive/physical function*, *safety*, *humanistic burden* (eg, patient-reported outcomes [PROs] and quality of life [QoL]), and *economic* and *disability outcomes*
- Search terms included:
  - *Clinical outcomes of annualized relapse rate (ARR)*, *disability progression*, and *magnetic resonance imaging (MRI) outcomes* and *health-related outcomes of QoL*, *work productivity*, *therapy persistence*, and *healthcare resource utilization (HCRU)*
- From a larger pool of studies representing a bigger group of key research questions and outcomes, a total of 27 publications were chosen to illustrate the following 3 points of interest and how they affect the MS disease course post-diagnosis:
  - Differences in MS outcomes by type of treatment (ie, high- vs low-efficacy therapy)
  - The value of early initiation of HET
  - The discrepancy in inclusion of (ie, discrepancy in definition of) certain DMTs as HET in the published literature

RESULTS

Included Studies

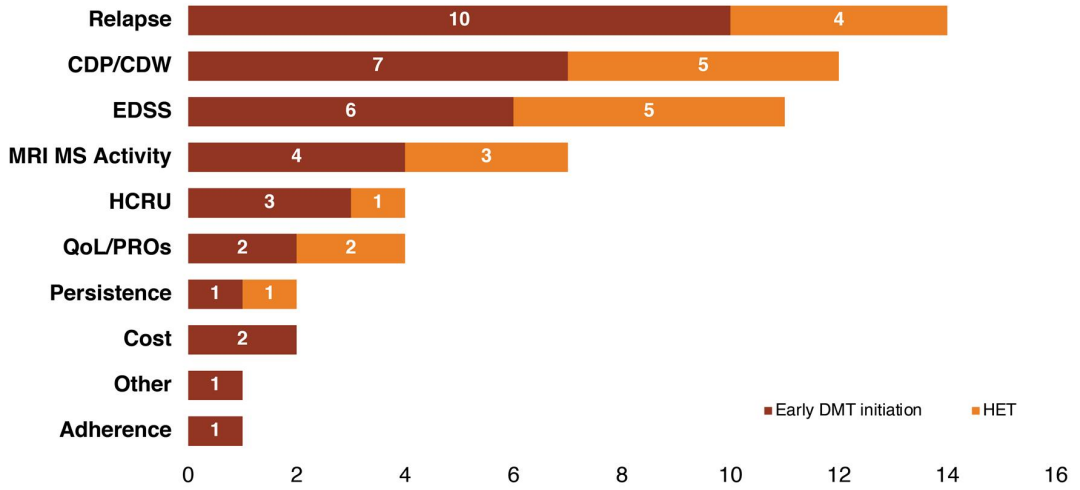
- Out of the 2,101 screened studies, 69 full-text studies were reviewed and 27 studies that reported on the impact of early DMT initiation and use of HET on clinical and health outcomes in patients with MS were included in this analysis.
  - Primary reasons for exclusion (42 studies) were as follows:
    - Evaluated moderate-efficacy or low-efficacy DMTs only (refer to definitions of DMT efficacy in **Table 5**)
    - Assessed a relationship between clinical and economic outcomes without regard to DMT efficacy level
    - Evaluated DMT benefit with no comparator regimen.
- The 27 articles included in this analysis reported on at least 1 of the parameters of interest:
  - Early DMT initiation
  - Use of HET (including a definition of HET, when available)
  - Clinical and health outcomes in patients with MS.
- A descriptive approach was used to group studies and identify trends.
  - **Figure 1**, **Figure 2**, and **Figure 3** provide details on study type, outcome, and DMT used, respectively, in the 27 included studies.
  - **Table 1** includes a brief summary of select outcomes for which a statistically significant treatment benefit was noted, grouped by parameter of interest (ie, early DMT, HET, or early HET) for the included studies.
- 18 of 27 studies consisted of real-world evidence, and relapse and disease progression were the most commonly included outcomes.
- Moderate- and low-efficacy injections were the most common DMTs that were included in studies.

Figure 1. Number of Studies by Study Type



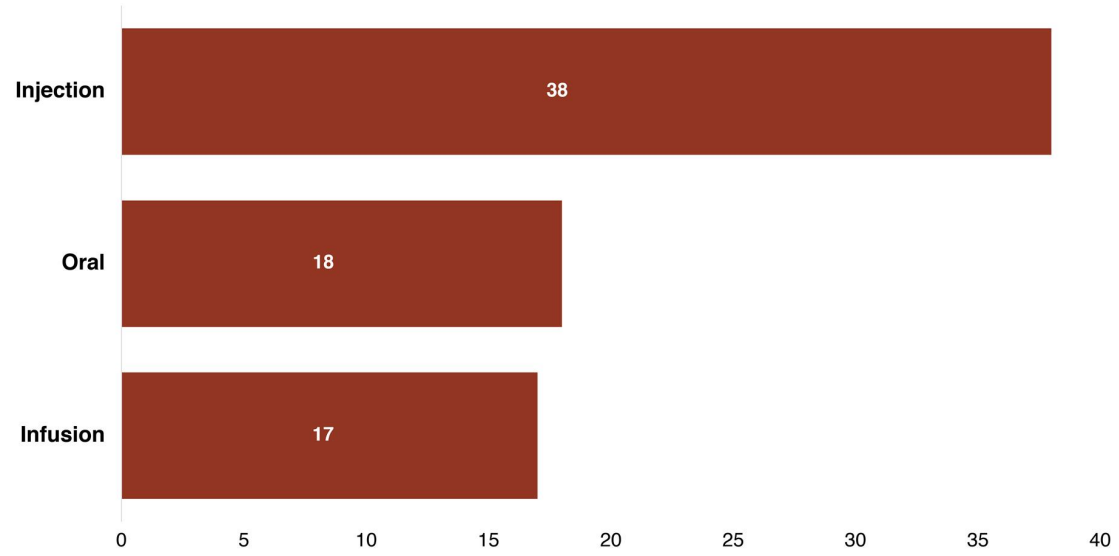
Key: DMT – disease-modifying therapy; HET – high-efficacy therapy; RCT – randomized controlled trial; RWE – real-world evidence; SLR – systematic literature review.

Figure 2. Number of Studies by Outcome[a]



[a] Studies included ≥1 outcome, so the total number of studies by outcome does not equate to 27 studies.
Key: CDP – clinical disease progression; CDW – clinical disease worsening; DMT – disease-modifying therapy; EDSS – Expanded Disability Status Scale; HCRU – healthcare resource utilization; HET – high-efficacy therapy; MRI – magnetic resonance imaging; MS – multiple sclerosis; PRO – patient-reported outcome; QoL – quality of life.

Figure 3. Number of Studies by Route of Administration[a]



[a] Studies included ≥1 outcome, so the total number of studies by outcome does not equate to 27 studies.

Clinical, Economic, and Patient-Reported Benefits of High-Efficacy DMT

- 11 of 27 studies addressed benefits of *both* HET and early DMT initiation.
  - HET:
    - 9 studies indicated a benefit for clinical outcomes
    - 2 indicated a benefit for humanistic burden including PROs and QoL
    - No studies were identified to indicate benefit of HET for economic outcomes
  - Early DMT initiation:
    - 22 studies indicated a benefit for clinical outcomes
    - 4 indicated a benefit for economic outcomes
    - 4 indicated a benefit for humanistic outcomes

RESULTS (CONT'D)

Table 1. Summary of Select Outcomes Included in the Analysis[a]

Parameter	ARR/CDP/ conversion to SPMS	MRI/BVL/lesion	QoL/work productivity	Persistence	Cost/HCRU
Early DMT	✔	✔	NA	✔	✔
HET	✔	✔	✔	✔	NA
Early HET	✔	✔	NA	NA	NA

Note: ✓ represents studies for which a statistically significant benefit was observed.
[a] Data are based on the studies included in the current literature review only.
Key: ARR – annualized relapse ratio; BVL – brain volume loss; CDP – clinical disease progression; DMT – disease-modifying therapy; HCRU – healthcare resource utilization; HET – high-efficacy therapy; MRI – magnetic resonance imaging; NA – not available; QoL – quality of life; SPMS – secondary progressive multiple sclerosis.

- Studies that included data on *early initiation of DMT, early HET, or both are* briefly summarized in **Table 2, Table 3,** and **Table 4**. Please contact the primary author for full details of these included studies (annie.chang@xcenda.com).
  - Clinical Outcomes for **Early DMT Initiation**
  - Patients who started DMT ≤2 years from clinical onset had lower mortality rates vs patients who delayed DMT start for 2 to 8 years (Chalmer 2018).
    - ARR was highest during childhood and 20 to 40 years of age (von Wyl 2020).
    - Accelerated brain atrophy starts early, often before MS diagnosis (Giovannoni 2010).
  - Improved Clinical Outcomes for **High-Efficacy DMTs**
    - Patients on interferon (IFN) β, glatiramer acetate, and teriflunomide were 1.6 times more likely to have relapses compared to patients on high-efficacy DMTs, such as fingolimod or natalizumab (Lo Re 2015).
    - Patients on ocrelizumab, a high-efficacy DMT, demonstrated a 94% reduction in gadolinium-enhancing T1 lesions, 80% reduction in new/newly enlarged hyperintense T2 lesions, and 31% less brain volume loss compared to patients on IFN β (Turner 2019).
    - Initial treatment with high-efficacy DMTs (fingolimod, alemtuzumab, or natalizumab) was associated with 34% lower risk of conversion to SPMS than initial treatment with glatiramer acetate/IFN β (Brown 2019).
    - Patients prescribed lower-efficacy (Betaseron, Rebif, Avonex, Copaxone, and Extavia [BRACE]) DMTs as a first treatment discontinued DMTs at a higher rate than those initially treated with HETs (natalizumab) (Jokubaitis 2013).
  - Improved Clinical Outcomes for **Early HET**
    - HETs exert their benefits over lower-efficacy treatments only during early stages of MS (Weideman 2017).
    - Initiating DMT early, and within 2 years of disease onset, results in significant long-term benefit for >5 years (He 2020).
    - The probability of converting to SPMS was 24% lower (significantly) for patients escalating from glatiramer acetate or IFN β to fingolimod, alemtuzumab, or natalizumab within 5 years of disease onset compared with matched patients escalated later (Brown 2019).
    - The ARR was 0.16 in the escalation group (moderate-efficacy injectables and orals) and 0.0 in the early intensive treatment group (high-efficacy monoclonal antibodies) (Harding 2019).
    - Initiating treatment with high-efficacy DMTs (eg, natalizumab) vs switching between BRACE decreased MRI activity by 45% (Prosperini 2012).
  - Economic Outcomes for **Early DMT Initiation**
    - Early DMT initiation results in cost savings (early vs delayed start for MS-related costs: $9,365 vs $13,661; $P<0.01$) and decreases hospitalizations (10.1% vs 16.5% for patients starting DMTs early vs delayed, respectively) (Curkendall 2011).
  - Humanistic Outcomes for **High-Efficacy DMT**
    - Patients on high-efficacy DMTs (eg, alemtuzumab) have shown significant improvements on functional and general QoL sustained through 2 years compared to patients on IFN β (Arroyo Gonzalez 2017).
    - Patients on high-efficacy DMTs were 2 to 3 times more likely to report improvements in work productivity and work attendance compared to BRACE patients (Chen 2018).

Early initiation of HET leads to better clinical outcomes and is associated with improved health-related outcomes

Table 2. Summary of Studies Reporting Clinical and Economic Outcomes With Early DMT Initiation[a]

Publication	Treatment(s)	Definitions	Key evidence/results (selected)
Mikaeloff 2008	IFN IM, IFN SC	No IFN, n=173 IFN, n=24	Patients receiving IFN experienced significantly fewer first attacks in the 1st and 2nd year of treatment (vs no treatment)
Giovannoni 2010	Cladribine	Cladribine 3.5 mg/kg (n=433) Cladribine 5.25 mg/kg (n=456) Placebo (n=437)	• Cladribine (both doses) had significantly lower **ARRs** vs placebo • **Relapse-free rate** was significantly higher for cladribine (both doses) vs placebo • Significant reductions were observed with cladribine (both doses) in the brain lesion count on MRI
Curkendall 2011	IFN IM, IFN SC, GA	Early DMT (before first documented MS), n=227; delayed DMT (started after documented MS), n=3,724	• MS-related costs were significantly lower in the early vs delayed start group • Hospitalizations occurred in significantly fewer patients starting DMTs early
Lampl 2012	IFN IM	Aged ≥50 years, n=68; <50 years, n=838 Aged ≥40 years, n=323; <40 years, n=583	• At baseline, patients ≥50 years had significantly higher EDSS scores • Patients ≥40 years and <40 years exhibited similar differences
Comi 2013	GA	Early GA (at randomization), n=198 vs delayed-treatment (placebo at randomization), n=122	• At entry into open-label phase, more patients in the delayed-treatment group had more **gadolinium-enhancing lesions** • Early treatment significantly **reduced CDMS conversion risk** • Over 5 years, more patients in the early treatment group were **relapse-free**
Kappos 2014	IFN SC	Cumulative dose exposure calculated by lowest and highest quartile Minimum cumulative dose group (mean [SD], 12.3 [7.4 mg]), n=73; maximum cumulative dose group (94.9 [10.4]), n=72	• Higher cumulative dose exposure and longer treatment time were associated with better time to **EDSS progression, change in EDSS**, and proportions of patients **with EDSS scores ≥4** or **≥6** • Change in EDSS from baseline to 24 months was a strong predictor of evaluated clinical outcomes over 15 years • Higher cumulative dose exposure was associated with better time to **conversion to SPMS** • Higher cumulative dose exposure and longer treatment time were associated with **better ARR outcome** at 15 years; each 5-year cycle of treatment provided a reduction in the mean ARR and risk of relapse
Zhornitsky 2015	IFN SC, IFN IM, GA	GA, n=906 IFN (combined), n=565	The study did not define "early" with respect to treatment initiation
Bachelet 2016	IFN SC, natalizumab	Aged >45 years and >50 years; number of patients varied by analysis at DMT	• Patients **aged >50 years** at start of IFN therapy developed **ADA** more frequently than adult patients **aged <30 years** • Patients **aged >45 years** at start of natalizumab therapy developed ADA more frequently than younger patients
Baruch 2016	IFN SC, alemtuzumab	DMT initiation for pediatric-onset MS (<18 years; n=51) or adult-onset MS (≥18 years; n=550)	**Age-adjusted SDMT scores** were significantly lower in pediatric-onset MS
Gold 2016	Dimethyl fumarate	Continuously treated with dimethyl fumarate for ≥6 years, n=144; placebo for 2 years then dimethyl fumarate for ≥4 years, n=85	• Greater **ARR risk reduction** was seen with earlier treatment initiation • Patients who delayed treatment and switched from placebo to dimethyl fumarate after 2 years had a significantly higher risk reduction • Similar data were reported for **confirmed disability progression** between the continuous and delayed treatment groups
Burks 2017	IFN IM, IFN SC, GA, dimethyl fumarate, fingolimod, natalizumab, teriflunomide	Total, N=12,431 Injectable, n=11,413 Oral, n=1,018	• Odds of **adherence** were significantly elevated with each year of age at index; there was no significant difference between adherence based on oral or injectable DMTs • Younger patients were significantly more likely to relapse
Corvino 2017	Not specified (all DMTs included)	Early initiators (≤90 days post-index), n=2,042; late initiators (>90 days), n=2,690	Significantly more late initiators experienced a relapse during the 2 years following MS diagnosis vs early initiators
Chalmer 2018	IVIg, minocycline, pulse steroid therapy, methotrexate, azathioprine, treosulfan, fingolimod, natalizumab, mitoxantrone, alemtuzumab	Early treatment (within 2 years of first MS symptoms), n=2,316 Later treatment (within 2–8 years after clinical onset), n=1,479	• Significantly more patients with later treatment start reached an **EDSS score of 6** vs the early-treated patients • Increased mortality in patients who started DMT treatment 2–8 years from clinical onset vs patients who started DMT treatment within 2 years
Salter 2018	Alemtuzumab, azathioprine, cyclophosphamide, daclizumab, dimethyl fumarate, fingolimod, IVIg, GA, IFN SC, IFN IM, laquinimod, methotrexate, mitoxantrone, mycophenolate mofetil, natalizumab, rituximab, peg-IFN, teriflunomide	"Early" not defined with respect to treatment initiation	• Both the PPMS and SPMS cohorts had a median level of disability, measured using the **PDDS** of 6 (bilateral support), 5 (late cane), or 7 (wheelchair/scooter) ! Statistical differences in distribution of disability levels between the cohorts existed and persisted after accounting for disease duration • Patients with PPMS and SPMS reported a median level of moderate **fatigue** and patients with RRMS reported a median level of mild fatigue • SPMS and PPMS cohorts had similar **severity of impairment** in the hand, vision, spasticity, and sensory domains ! Impairment generally one level higher than in the RRMS cohort with the exception of vision • The median level of the **cognition performance scale** was lower in the PPMS and RRMS cohorts compared to the SPMS cohort
Haas 2019	IFN IM, fingolimod	**FREEDOMS/ FREEDOMS II** Early (immediate) fingolimod initiation in core phase (years 1–2), n=783; extension phase (years 3–4), n=561 Delayed fingolimod initiation in core phase, n=773 (placebo); extension phase, n=526 (fingolimod) **TRANSFORMS** Early fingolimod in core phase (year 1), n=429; extension phase (year 2), n=356 Delayed fingolimod in core phase, n=431 (IFN IM); extension phase, n=341 (fingolimod)	**FREEDOMS/ FREEDOMS II** • At year 2, **ARR** (all relapse categories) showed significant reductions with immediate fingolimod • At 4 years, ARR remained low (all relapse categories) with immediate fingolimod; the risk was significantly lower for **severe relapses** vs placebo • The delayed fingolimod group showed significantly stronger reductions in all categories of relapses at years 3–4 after switching to fingolimod following 2 years of placebo **TRANSFORMS** At year 1, **ARR** (all relapse categories) showed significant reductions with immediate fingolimod vs IFN The delayed fingolimod group showed stronger reductions (all relapse categories) at year 2 after switching, with significant differences observed for **severe relapses, relapses requiring steroid use**, and impact of relapses on **activities of daily living**
Von Wyl 2020	IFN (not specified), GA	Pediatric onset, n=236 Adult onset, n=9,469	• Pediatric-onset MS group reached specific **EDSS milestones** after a longer period than adult-onset MS patients • **Risk for relapses** was highest in childhood and decreased continuously to ~35 years • **Disability worsening** remained stable from childhood to ~32 years and then increased sharply at ~45 years

[a] Please contact the primary author for full details of these included studies (annie.chang@xcenda.com).

Key: ADA – anti-drug antibody; ARR – annualized relapse rate; CDMS – clinically definite multiple sclerosis; DMT – disease-modifying therapy; EDSS – Expanded Disability Status Scale; GA – glatiramer acetate; HCRU – healthcare resource utilization; IFN – interferon; IM – intramuscular; IV – intravenous; IVIg – intravenous immunoglobulin; MRI – magnetic resonance imaging; MS – multiple sclerosis; PDDS – patient-determined disease steps; PPMS – primary progressive multiple sclerosis; RRMS – relapsing remitting multiple sclerosis; SAD – sustained accumulation of disability; SC – subcutaneous; SD – standard deviation; SDMT – Symbol Digit Modalities Test; SPMS – secondary progressive multiple sclerosis.

Table 3. Summary of Studies Reporting Clinical and Economic Outcomes With HET and/or Early DMT Initiation[a]

Publication	Treatment(s)	Definitions	Key evidence/results (selected)
Jokubaitis 2013	IFN IM, IFN SC, natalizumab, GA	"Early" not defined with respect to treatment initiation	• Younger age at treatment initiation and higher **EDSS** were predictive of DMT discontinuation • Treatment with natalizumab as a subsequent DMT **led to** significantly longer time on treatment (compared to IFN or GA) • Annualized **switch or cessation rates** were lower for natalizumab
Johnson 2015	IFN IM, IFN SC, GA, natalizumab	Platform therapy, n=882 Natalizumab, n=882	• **Relapse** occurred among significantly fewer patients in the natalizumab group • Relapses were significantly later for patients on natalizumab
Lo Re 2015	First-line therapies (IFN, GA, teriflunomide, azathioprine), second-line therapies (natalizumab, fingolimod)	"Early" not defined with respect to treatment initiation	• Lower risk of **relapse** with natalizumab and fingolimod treatment vs IFN, GA, teriflunomide, or azathioprine • More **clinical and radiological reactivation** was observed in the therapy-free and first-line therapy (IFN, GA, teriflunomide, azathioprine) groups
Arroyo Gonzales 2017	IFN SC, alemtuzumab	CARE-MS I IFN: n=187 Alemtuzumab: n=376 CARE-MS II IFN: n=202 Alemtuzumab: n=426	• Significantly greater **QoL** improvements for alemtuzumab over IFN SC were seen at all time points in: ◦ CARE-MS II with **FAMS , EQ-5D** visual analog scale, and **SF-36** physical component summary ◦ CARE-MS I with FAMS
Weideman 2017	IFN (type not specified), GA, fingolimod, dimethyl fumarate, teriflunomide, mitoxantrone, daclizumab, natalizumab, alemtuzumab, rituximab, ocrelizumab, laquinimod, siponimod	"Early" not defined with respect to treatment initiation	• Efficacy of immunomodulatory DMTs on MS disability strongly decreased with advancing age • High-efficacy drugs outperformed low-efficacy drugs in inhibiting MS disability for patients aged <40.5 years • At >53 years, the model suggests there is no predicted benefit to receiving immunomodulatory DMTs
Chen 2018	IFN IM, IFN SC, GA, dimethyl fumarate, fingolimod, natalizumab, alemtuzumab, teriflunomide	Category 1 DMTs (IFN, GA): n=706 Category 2 DMTs (teriflunomide, dimethyl fumarate): n=187 Category 3 DMTs (fingolimod, natalizumab, alemtuzumab, mitoxantrone): n=491	• Patients on Category 3 DMTs (vs injectable DMTs) were more likely to report improvements in: ◦ **amount of work** ◦ increased **work attendance,** ◦ **work productivity**
Turner 2019	IFN SC, ocrelizumab	IFN: n=829 Ocrelizumab: n=827 Analyses were also performed for patients aged <40 years and ≥40 years	Ocrelizumab demonstrated a significant reduction in treatment-by-subgroup interactions for **ARR** by age (<40 vs ≥40 years) Ocrelizumab significantly reduced **disease progression** at 12 and 24 weeks Ocrelizumab significantly reduced average number of **gadolinium-enhancing T1 lesions** and new or newly-enlarged hyperintense T2 lesions per scan Ocrelizumab showed significant treatment-by-subgroup interactions (<40 vs ≥40 years) Ocrelizumab demonstrated significant benefit in change from baseline **brain volume**N The increase in the proportion of patients with **NEDA** with ocrelizumab was significantly higher

[a] Please contact the primary author for full details of these included studies (annie.chang@xcenda.com).

Key: ARR – annualized relapse rate; DMT – disease-modifying therapy; EDSS – Expanded Disability Status Scale; FAMS – Functional Assessment of Multiple Sclerosis; GA – glatiramer acetate; HET – high-efficacy therapy; IFN – interferon; IM – intramuscular; MS – multiple sclerosis; NEDA – no evidence of disease activity; QoL – quality of life; SC – subcutaneous; SF-36 – 36-Item Short-Form Survey.

Table 4. Summary of Studies Reporting Clinical and Economic Outcomes With Early HET[a]

Publication	Treatment(s)	Definitions	Key evidence/results (selected)
Prosperini 2012	IFN IM, IFN SC, natalizumab, GA	Escalation to second-line natalizumab, n=106 Switching among immunomodulators (IFN or GA), n=161	More patients on an escalation regimen experienced absence of the following parameters at 12 and 24 months (statistically significant difference at 24 months only): • **Relapses** • **Sustained EDSS progression** • **MRI activity** • **Any disease activity**
Brown 2019	IFN (type not specified), GA, fingolimod, natalizumab, alemtuzumab	Initial treatment with GA or IFN and escalation to fingolimod, alemtuzumab, or natalizumab (HET) ≤5 years, n=307; >5 years, n=331	• **Initial treatment with HET vs GA or IFN was associated with a lower risk of conversion to SPMS**
Harding 2019	IFN IM, IFN SC, GA, dimethyl fumarate, fingolimod, natalizumab, alemtuzumab, teriflunomide	HET/early intensive treatment, n=104 Moderate-efficacy DMT/escalation, n=488	• Mean 5-year change in **EDSS** score was lower in the early intensive treatment group • The majority of those who escalated to high-efficacy DMTs developed **SAD** while still receiving initial moderate-efficacy treatment pre-escalation
He 2020	Rituximab, fingolimod, natalizumab, alemtuzumab, teriflunomide	HET initiated early (0□2 years, n=277) or late (4□6 years, n=267) after disease onset	• In the 6th and 10th years after disease onset, the mean **EDSS** scores were significantly lower in the early HET group

[a] Please contact the primary author for full details of these included studies (annie.chang@xcenda.com).

Key: DMT – disease-modifying therapy; EDSS – Expanded Disability Status Scale; GA – glatiramer acetate; HET – high-efficacy therapy; IFN – interferon; IM – intramuscular; MRI – magnetic resonance imaging; NEDA – no evidence of disease activity; SAD – sustained accumulation of disability; SC – subcutaneous; SPMS – secondary progressive multiple sclerosis.

- Studies reporting on the definition used for HET can be found in **Table 5.** The definition itself is included for reference.
  - 4 of 27 studies defined DMT efficacy level and specified DMTs categorized into each efficacy level.
  - Efficacy levels and DMTs within each efficacy level were inconsistent.
    - Efficacy levels were defined using terms including "category," "high- or low-efficacy," and "not high-efficacy," and efficacy category names differed across studies.
    - Infused DMTs were typically defined as HET; however, inconsistencies in defining efficacy level were found especially for fingolimod and dimethyl fumarate, which were grouped as HET and moderate-efficacy therapy.
      - Fingolimod was defined as low-efficacy, moderate-efficacy, high-efficacy, and not high-efficacy in 1 study each.
      - Dimethyl fumarate and teriflunomide were defined as low-efficacy and not high-efficacy in 1 study each and moderate-efficacy in 2 studies.

Table 5. HET Definitions

Publication	Treatments and definitions
Weideman 2017	High-efficacy: Ocrelizumab, mitoxantrone, alemtuzumab, daclizumab, natalizumab Low-efficacy: Fingolimod, dimethyl fumarate, interferon, teriflunomide, glatiramer acetate
Chen 2018	Category 1 efficacy: Interferon, glatiramer acetate Category 2 efficacy: Teriflunomide, dimethyl fumarate Category 3 efficacy: Fingolimod, natalizumab, alemtuzumab, mitoxantrone
Harding 2019	High-efficacy: Alemtuzumab, natalizumab Moderate-efficacy: Interferon, glatiramer acetate, dimethyl fumarate, fingolimod, teriflunomide
He 2020	High-efficacy: Rituximab, ocrelizumab, mitoxantrone, alemtuzumab, natalizumab Not high-efficacy: Interferon, glatiramer acetate, oral DMTs (fingolimod, teriflunomide, dimethyl fumarate, cladribine)

Key: DMT – disease-modifying therapy.

LIMITATIONS AND CONCLUSION

Limitations

- The literature review was targeted in nature; therefore, some relevant publications may have been missed.
- The majority of included publications were from observational studies and may therefore suffer from biases inherent to these types of studies.
- Studies were heterogeneous, reporting on a variety of outcomes, populations, and data sources, limiting the ability to meaningfully synthesize data.

Conclusion

- Emerging evidence suggests that initiating HET vs lower-efficacy treatments leads to improved outcomes in patients with MS.
- Furthermore, early initiation of HET leads to better clinical outcomes and is associated with improved health-related outcomes.
- However, the data are limited, and a need exists to better understand the humanistic and economic benefits of initiating HET early in the MS disease course.
- In addition, there is a need to better standardize the definition of HET to inform treatment decision making for patients and providers.

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Please contact Annie Chang at annie.chang@xcenda.com for the full reference list.

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