Initial high-efficacy disease-modifying therapy in multiple sclerosis. A nationwide cohort study

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Search terms: [41] Multiple sclerosis, [54] Cohort studies [23] Clinical trials Observational

study (Cohort, Case control)

Title: 96 characters
Abstract: 236 words
Main paper: 4361 words
No. of references: 38
No. of tables: 1
No. of figures: 5

The statistical analysis was conducted by the first author, Mathias Buron (Danish Multiple Sclerosis Center, University of Copenhagen Hospital Rigshospitalet, Copenhagen, Denmark)

There is no supplementary data to the manuscript.

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Declaration of conflicting interests

MD. Buron has received support for congress participation from Roche.

TA. Chalmer has received support for congress participation from Merck, Novartis, Biogen, and Roche.

F. Sellebjerg has served on scientific advisory boards, been on the steering committees of clinical trials, served as a consultant, received support for congress participation, received speaker honoraria, or received research support for his laboratory from Biogen, EMD Serono, Merck, Novartis, Roche, Sanofi Genzyme, and Teva.

MK. Christensen has received a research grant from Novartis, and has received support for congress participation from Biogen, Merck, Roche and Teva.

V. Hansen has received support for congress participation from Roche, Biogen, Merck, Sanofi Genzyme, and Almirall.

Z. Illes has served on scientific advisory boards, served as a consultant, received support for congress participation, received speaker honoraria, and received research support from Biogen, Merck-Serono, Sanofi-Genzyme, Lundbeck, and Novartis.

HB. Jensen has served on the scientific advisory board for Biogen Idec and Novartis, and has received honoraria for lecturing and support for congress participation from Biogen Idec and Novartis.

M. Kant has received support for congress participation from Novartis, Genzyme, Teva, and Roche.

V. Papp has received support for scientific meetings from Merck and Sanofi-Genzyme.

T. Petersen has received research grant support from Biogen, Merck, Novartis, Sanofi, Alexion, Roche, and Genzyme.

PV. Rasmussen has received speaker honoraria from TEVA, Biogen, Roche and Novartis, support for congress participation from Merck, Roche, Sanofi and TEVA, fees for serving on advisory boards from Merck, Roche, Novartis, Biogen, and Sanofi.

J. Schäfer has received travel support for congress participation from Genzyme, Roche, Merck, Teva, Biogen.

Á. Theódórsdóttir has served on a scientific advisory board, received support for congress participation, and received research support from Biogen, Roche, Sanofi-Genzyme and Novartis.

A. Weglewski has served on scientific advisory board for Merck, has received honoraria for lecturing from Sanofi-Genzyme, and has received support for congress participation from Biogen, Genzyme, Teva, and Merck.

PS. Sorensen has received personal compensation for serving on advisory boards for Biogen, Merck, Novartis, Teva, MedDay Pharmaceuticals and GSK; on steering committees or independent data monitoring boards in trials sponsored by Merck, Teva, GSK, and Novartis; and has received speaker honoraria from Biogen, Merck Serono, Teva, Sanofi-Aventis, Genzyme, and Novartis.

M. Magyari has served on scientific advisory board for Biogen, Sanofi, Teva, Roche, Novartis, Merck, has received honoraria for lecturing from Biogen, Merck, Novartis, Sanofi, Genzyme, has received support for congress participation from Biogen, Genzyme, Teva, Roche.

J. Romme Christensen, **D. Bech**, **S. Prakash** and **I. Barzinji** report no disclosures.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Abstract

Objective: To determine the effectiveness of high-efficacy disease-modifying therapies (heDMT) versus medium-efficacy disease-modifying therapies (meDMT) as the first treatment choice in treatment-naïve patients with multiple sclerosis (MS) on disability worsening and relapses. We assessed this using a nationwide population-based MS registry.

Methods: We identified all patients starting a heDMT as first-time treatment from the Danish Multiple Sclerosis Registry and compared treatment outcomes with a propensity-score matched sample of patients starting meDMT.

Results: We included 388 patients in the study: 194 starting initial therapy with heDMT matched to 194 patients starting meDMT. At 4 years of follow-up, the probabilities of a 6-month confirmed Expanded Disability Status Scale (EDSS) score worsening were 16.7% (95% confidence interval (CI): 10.4%-23.0%) and 30.1% (95% CI: 23.1%-37.1%) for heDMT- and meDMT-initiators, respectively (Hazard ratio (HR): 0.53, 95% CI 0.33-0.83, p=0.006). Patients initiating heDMT also had a lower probability of a first relapse (HR 0.50, 95% CI 0.37-0.67). Results were similar after pairwise censoring and in subgroups with high-baseline activity, diagnosis after year 2006 or information on baseline T2 lesion load.

Conclusion: We found a lower probability of 6-month confirmed EDSS score worsening and lower probability of a first relapse in patients starting a heDMT as first therapy, compared to a matched sample starting meDMT.

Classification of Evidence:

This study provides Class III evidence that for patients with MS, starting heDMT lowers the risk of EDSS worsening and relapses compared to starting meDMT.

Introduction

Disease modifying therapies (DMT) for relapsing-remitting multiple sclerosis (RRMS) are divided into moderate-efficacy disease-modifying therapies (meDMT) and high-efficacy disease-modifying therapies (heDMT) based on their ability to reduce relapse rates, MRI disease activity, and disability worsening. In general, the heDMT pose an increased risk of more serious adverse events compared to the meDMT.[1]

Treatment with DMT has been shown in randomized clinical trials to be associated with a beneficial effect on relapses, disability accumulation, and transition to secondary progressive disease[2–6]. Observational studies have shown improved long-term disability outcomes in patients starting early treatment with DMT, compared with a later treatment start.[7,8]

Current treatment paradigms recommend starting with a meDMT in patients presenting with average disease activity and escalation of therapy to a heDMT after a suboptimal treatment response to a meDMT. More aggressive therapy, initiating a heDMT as the first treatment, is often reserved for a minority of patients with frequent and severe relapses or high disease activity on MRI scans[9,10]. This is reflected in a recent treatment guideline recommending start of an heDMT as first choice in patients presenting with highly active RRMS[9]. This recommendation is based on subgroup analyses from the phase III pivotal trials of alemtuzumab, fingolimod, and natalizumab[11–15]. During recent years, several papers have recommended to start early high-efficacy treatment in patients with high disease activity[16,17].

However, evidence of an improved prognosis when initiating active patients directly on a heDMT compared with the usual escalation regimen is scarce. This study investigates the effect of starting on a heDMT as the first choice compared with starting on a meDMT initially, in a propensity score-based matched sample.

Methods

Data sources

In Denmark, the health-care system is government-financed with free and equal access for all citizens. Danish citizens are given a unique and permanent civil registration number at birth or immigration, which allows cross-linkage of data at the individual-level from nationwide registers.[18]

DMT is provided free of charge in Denmark at 14 public MS clinics, and it is mandatory for all treating clinics to report clinical data to The Danish Multiple Sclerosis Registry (DMSR). This ensures high completeness and high data density, and the registry encompasses nearly every patient treated with DMT in Denmark.

The DMSR holds data on diagnosis, disease course, treatment, clinical visits, Expanded Disability Status Scale (EDSS) scores, relapse dates, adverse effects, MRI parameters and reasons for treatment discontinuation. In all 14 Danish MS clinics, the treating physician enters data directly into the DMSR using an online platform. Data on T2 lesion load on MRI are entered by the treating neurologist at clinical visits according to the neuroradiologist' report and categorized as: 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10-20 and >20 lesions. The interval for data entries is at treatment start and at all follow-up visits, which are at 3 and 6 months, and then every 6 months after treatment start.

We obtained data on sex, date of birth, death, and emigration from the Danish Central Person Registry, and cross-linked the data to the DMSR on an individual level.

Study population and outcomes

All patients with RRMS according to the 2001 or 2010 McDonald criteria[19,20], who initiated first-time DMT from 2001 and until the time of data extraction (May 6^{th,} 2018), were identified. Exclusion criteria at baseline were age under 18 years at treatment start, baseline EDSS above 5.5,

missing relapse rate in the previous 2 years, missing baseline EDSS, or initiation of off-label therapy. Patients without a minimum of 2 post-baseline EDSS scores at least 6 months apart were also excluded, as they did not have an even theoretical probability of meeting the primary outcome.

Patients were observed from the initiation of first treatment start and until death, emigration or the date of their last visit with a valid EDSS score. Patients without a visit with an associated EDSS score for 3 years were considered lost to follow-up and censored at the time of their last recorded EDSS score. We defined heDMT according to the EMA classification of second-line therapies as natalizumab, fingolimod, alemtuzumab, cladribine, daclizumab, or ocrelizumab. We defined meDMT as interferon-β, teriflunomide, dimethyl fumarate, or glatiramer acetate. Off-label therapy included methotrexate, treosulfan, rituximab, ofatumumab, monthly methylprednisolone pulse therapy, intravenous human immunoglobulin therapy, mitoxantrone, or autologous hematologic stem-cell transplantation.

The primary outcome was time to 6-month confirmed EDSS worsening. EDSS worsening was defined as a sustained increase in EDSS score confirmed on two consecutive visits at least 6 months apart. The required increase was defined as: ≥1.5 in patients with a baseline EDSS score of 0, and ≥1 point in patients with a baseline EDSS score of 1 or above. We defined our outcome date as the date of the first EDSS-worsening (and not the confirmation date). The assigned level of evidence for this outcome was class III.

The secondary outcome was time to first on-treatment relapse. We defined time to first relapse as the interval between treatment start and the first occurrence of a relapse, while on their first treatment. Accordingly, for this outcome, an additional censoring event was the occurrence of a switch or termination of treatment. The assigned level of evidence for this outcome was class III.

To evaluate the effects of potential attrition bias, we performed a sensitivity analysis of the primary outcome using pair-wise censoring within the matched pairs. Consequently, the follow-up time for each patient in the same pair was determined by the shortest of the 2 follow-up periods. We also performed a sensitivity analysis matching on the original, global multiple sclerosis severity score (MSSS).[21]

To assess the robustness of results, we performed analyses of the primary endpoint in the following subgroups: (1) patients with high baseline disease activity; (2) patients diagnosed from 2006 and onwards; (3) patients with >4 post-baseline EDSS assessments; (4) analyses with fingolimod redefined as a meDMT; and (5) patients additionally matched on baseline T2 lesion load.

High baseline disease activity was defined as ≥3 relapses within 2 years before baseline, or ≥2 relapses within 1 year before baseline.

The reason for choosing to assess the primary outcome in a population initiating their first-time DMT from 2006 and onwards was that the first heDMT in Denmark was marketed in 2006.

For the MRI subgroup, we only included patients with a valid baseline MRI. This was defined as a registered MRI with valid data on T2 lesion amount within 3 months prior to the start of treatment. If multiple valid baseline MRIs were available, the one performed nearest to the baseline date was used.

Statistical analysis

We identified patients initiating first-time treatment with heDMT and propensity-score matched them to patients initiating treatment with meDMT using nearest neighbor matching with a fixed match ratio of 1:1. To ensure acceptable similarity of matched subjects, the matching was restricted by a caliper of 0.1 standard deviations of the logit-transformed propensity score[22]. We evaluated and ensured acceptable common support of the propensity score and validated the model

assumptions of the logistic regression model defining the propensity-score. We assessed the balancing effect of the propensity-score matching using standardized differences of all the included variables, considering a standardized difference below 0.1 as indicating acceptable balance.[23] Included baseline variables in the propensity-score model for main analyses were age, sex, prior 24-month relapse count, EDSS score, and disease duration.

We reported descriptive continuous baseline variables using means and standard deviations (SD) or medians and interquartile ranges (IQR), as appropriate. Binary variables were described using counts and percentages.

For the primary and secondary outcomes, we estimated probabilities of the outcomes using non-parametric Kaplan-Meier estimation. Absolute risk reductions and numbers needed to treat (NNT) were calculated for both main analyses[24]. We analyzed rates using semi-parametric Cox-proportional hazards models with robust variance estimation to account for the matching. The proportional hazards assumptions were visually checked by cumulative Martingale residuals and statistically with the Kolmogorov supremum-test on 1000 resamples. The primary outcome was formally tested for difference using the log-rank test for difference in absolute probabilities, and a type 3 test for difference in rates. As a sensitivity analysis, we then performed the EDSS worsening analyses with pair-wise censoring to investigate potential effects of attrition bias. For the MSSS-analysis, we included the MSSS-score as a continuous variable in the propensity score matching instead of baseline EDSS and disease duration, and calculated hazard rate ratios using Cox regression models.

For all the subgroup analyses, we performed new propensity score matchings, as described above, using only patients meeting the required criteria for the individual analyses. We quantitively assessed any difference in rates in these subgroups by calculating hazard ratios using a robust

variance Cox-proportional hazards model for the primary outcome. We checked balancing and model assumptions for all analyses, as also described for the main analysis. For the pairwise censoring analysis, we additionally performed Kaplan-Meier estimation, as described previously, to depict absolute probabilities of the outcomes. For the MRI analysis, the number of baseline T2 lesions was entered in the propensity score as a categorical parameter, categorized as noted above.

We performed all analyses using SAS software, version 9.4 (SAS Institute, Inc., Cary, North Carolina, USA). Original MSSS was calculated using R (R Core Team (2013), Vienna, Austria.) using the "ms.sev" package[25].

Ethics

This study was approved by the Danish Data Protection Agency (journal no. RH-2017-347, I-Suite no: 06058). Non-interventional register-based studies do not require ethical approval in Denmark.

Data availability

Anonymized data will be shared on request from any qualified investigator under approval from the Danish Data Protection Agency and the board of the Danish Multiple Sclerosis Registry.

Results

A total of 8,953 patients started a first-time DMT from 2001 and onwards. The proportions of these patients starting on a heDMT as first ever therapy according to calendar year are shown in **figure 1**. In the full cohort, 6,528 patients were eligible for matching. Of these, 195 patients started treatment with a heDMT.

A total of 194 patients starting with heDMT were 1:1 matched with 194 patients starting meDMT (**figure 2**)**.** Baseline characteristics between groups were similar, as seen in **table 1.**

Our propensity score model was assessed, and we found acceptable common support of the propensity scores. Further, when assessing the balance of the matched sample, all the included variables in the propensity-score model had a standardized difference of less than 0.1 between exposure groups, indicating a well-specified propensity score model with good balancing of baseline variables. The model reported higher chance for heDMT treatment with lower age (odds ratio (OR) 0.96 95% confidence interval (CI): 0.95-0.98), increasing baseline EDSS (OR 1.60, 95% CI: 1.42-1.81), increasing baseline relapse rate (OR 1.35 95% CI: 1.20-1.52), and shorter baseline disease duration (OR 0.96, 95% CI: 0.93-0.99). Female sex was associated with lower propensity for heDMT (OR 0.92, 95% CI: 0.68-1.26).

The total follow-up time was 2059 years with each patient contributing on average 5.3 years (SD 3.8, range: 0.3-16.9 years). A total of 4308 valid EDSS scores were available during follow-up, averaging 2.36 and 2.28 visits per year of follow-up for the heDMT and meDMT-groups, respectively. Of these 4308 EDSS scores, 75.8% were performed within 6 months from the preceding score, without any noticeable difference between groups (78.3% vs 74.3% for heDMT and meDMT, respectively). The proportions of patients with at least 2 visits per year on average were 62.9% and 49.7% in the heDMT- and meDMT-group, respectively.

During follow-up, 75 patients (38.7%) in the meDMT-group escalated to heDMT after a mean of 3.1 years. A total of 165 relapses and 103 6-month confirmed EDSS-worsening events occurred during follow-up.

In the primary outcome of time to 6-month confirmed EDSS worsening, the absolute probabilities of an occurrence of an event at 2 and 4 years of follow-up were 18.3% (95% CI: 12.7%-23.9%) and 30.1% (95% CI: 23.1%-37.1%) in the meDMT-initiators, with the heDMT-initiators having corresponding probabilities of 11.5% (95% CI: 6.7%-16.3%) and 16.7% (95% CI: 10.4%-23.0%).

The absolute risk reductions at 2 and 4 years were 6.8% (95% CI: -0.01%-14.1%) and 13.5% (95% CI: 4.0%-22.9%), corresponding to a number needed to treat (NNT) of 14.7 and 7.4, respectively. The event probabilities between exposure groups differed statistically significantly (p=0.0049). For details and confidence intervals, see the Kaplan-Meier plot **in figure 3**. The heDMT-group had a 47% lower rate of EDSS worsening compared with the meDMT-group (hazard ratio (HR) 0.53, 95% CI 0.33-0.83, p=0.006). In the sensitivity analysis using pair-wise censoring, both the risk difference (**figure 4)** and rate ratio (HR 0.49, 95% CI 0.29-0.83) were comparable to the main results. In the sensitivity analysis adjusting for MSSS results were similar (HR 0.56, 95% CI 0.37-0.86). Matching on MSSS also induced balance across groups on disease duration and baseline EDSS.

In the secondary outcome of time to first relapse, the absolute probabilities of an event at 2 and 4 years of follow-up were 51.8% (95% CI: 43.8%-59.8%) and 66.9% (95% CI: 58.1%-75.8%) in the meDMT-group and 30.6% (95% CI: 23.5%-37.7%) and 41.4% (95% CI: 32.7%-50.0%) in the heDMT-group. The absolute risk reductions at 2 and 4 years were 21.2% (95% CI: 10.5%-31.9%) and 25.6% (95% CI: 13.2%-38.0%), corresponding to a NNT of 4.7 and 3.9, respectively. For details, see the Kaplan-Meier plot in **figure 5.** The heDMT-group had a 50% lower rate of a first relapse when compared with the meDMT-group (HR 0.50, 95% CI 0.37-0.67).

Subgroup analyses

We tested whether including only patients with a high baseline disease activity would change the result. From the total cohort, 1591 patients fulfilled the criteria for high baseline disease activity when initiating first-ever therapy. Of these, 266 patients were excluded according to the previously defined exclusion-criteria, leaving 1,325 patients who were eligible for matching. Among these, 108 patients started heDMT as first therapy. After propensity score matching, a total of 106 heDMT

patients were successfully matched to 106 patients starting meDMT. In this analysis, the heDMT-group showed a 52% lower rate of EDSS worsening compared with the meDMT-group (HR 0.48, 95% CI: 0.25-0.91). Similarly, the heDMT-group had a 40% lower rate of a first relapse compared with the meDMT-group (HR 0.60, 95% CI: 0.42-0.85).

In patients starting first-time DMT from the year 2006 and onwards, a total of 4,968 patients were eligible for matching, among these all 195 patients starting first-time heDMT. In this group, 884 patients (17.8%) had a high baseline disease activity, as defined previously. After matching, a total of 191 pairs were successfully matched. In the meDMT-group 39.3% escalated to heDMT treatment during follow-up, after a mean of 2.7 years. In this analysis, the heDMT group also showed a lower rate of EDSS worsening (HR 0.67, 95% CI 0.43-1.05) compared with the meDMT-group.

The difference between groups was comparable to the main analysis when re-classifying fingolimod as a meDMT with the heDMT-group having a 53% lower rate of 6-month confirmed EDSS worsening (HR 0.47, 95% CI 0.26-0.84).

A total of 7151 patients were eligible for matching when only including patients with a minimum of 4 post-baseline EDSS measurements, of which 159 started heDMT. After matching, all 159 heDMT-initiators were matched to corresponding patients starting meDMT. Results were similar to the heDMT group having 42% lower rate of 6-month confirmed EDSS worsening, compared with the meDMT-group (HR 0.58, 95% CI 0.37-0.93).

In the MRI subgroup, a total of 1244 patients with a valid baseline MRI were eligible for matching, of which 97 started heDMT. These were all successfully matched to 97 meDMT-initiators. Most patients in the matched sample had either 10-20 lesions (30.9%) or >20 lesions (53.6 %). Results in this analysis were comparable to the main analysis with the heDMT-group having a 42 % lower rate of EDSS worsening compared to the meDMT-group (HR 0.58, 95% CI 0.26-1.27).

Classification of evidence

This study provides Class III evidence that for patients with MS, starting heDMT lowers the risk of EDSS worsening and relapses compared to starting meDMT.

Discussion

We aimed at investigating the effectiveness of initial high efficacy disease-modifying therapy (heDMT) compared with initial moderate efficacy disease-modifying therapy (meDMT) in a propensity-score matched cohort of patients from the nationwide, population-based Danish Multiple Sclerosis Registry. We found a lower risk of 6-month confirmed EDSS worsening and a lower risk of a first relapse in patients, who started directly on a heDMT compared with patients starting on a meDMT. The results were similar after pair-wise censoring and matching for MSSS. We performed a subgroup analysis of patients meeting the criteria for high disease activity at baseline to better assess the treatment effect in patients who were more likely to be targets for initial heDMT in Denmark. We found comparable results as in the main analysis, with the estimate suggesting a tendency towards a higher benefit of initial heDMT in these patients. This result was not surprising as this subgroup represents patients with a higher inflammatory activity, where heDMT would likely show a larger effect. The subgroup analysis only including patients starting treatment after 2006 also showed a favorable outcome in the heDMT-group. We conducted this analysis to assess the effect of initial heDMT treatment in a setting where access to escalation of treatment was available for all patients with disease activity on a meDMT. Interestingly, in this period with accessibility to heDMT, only 22% of patients fulfilling our criteria for high baseline disease activity were started directly on heDMT. Further, redefining the efficacy status of fingolimod or restricting the inclusion criteria to at least 4 post-baseline EDSS assessments did not change the results.

Finally, results were similar when controlling for baseline T2 lesion load on MRI in a sub-group of patients with available MRI data.

Interestingly, we observed an increase in the use of heDMT in treatment-naïve patients with increasing calendar-year. This may be due to a combination of increasing emphasis on treatment efficacy, less tolerance to any residual disease activity, and more cumulated clinical experience in using the newer, more effective heDMT. Further, updates to the Danish treatment guidelines have included a recommendation of starting patients with perceived high clinical and radiological disease activity directly on heDMT.[26] A common interpretation of high disease activity is having 2 or more severe relapses within 12 months and severe radiological activity. In the duration of our inclusion period, the Danish treatment guideline has stated that the default drugs of choice in John Cunningham Virus (JCV)-negative patients is natalizumab, while JCV-positive patients should be offered fingolimod – if there are no specific contraindications to these drugs. This is also reflected in the heDMT-group of this study, which is almost entirely consisting of patients starting natalizumab or fingolimod.

For patients with average disease severity, current treatment paradigms recommend an escalation-based approach where patients are initially started on a meDMT and, in the case of disease breakthrough, escalate to a more efficacious therapy. The main argument for choosing an escalation-type approach is stronger evidence regarding the safety profile of meDMT. We were not able to meaningfully compare characteristics and severity of adverse events between the study groups, which makes our study unable to explore all potential nuances required by a cost-benefit analysis of choosing either of the two treatment approaches. However, our results provide estimates of the treatment effect of starting initial heDMT compared to meDMT in patients with clinical characteristics identical to those patients who actually started directly on heDMT — a concept termed “the average treatment effect of the treated”.[27]

Disease activity early in the disease course is associated with an unfavorable long-term risk of disability and increased risk of conversion to SPMS[28–30]. Further, systemic inflammatory activity is a more predominant mechanism of the disease earlier in the disease course when compared with the more complex pathogenesis in late-stage MS, which is also evidenced by the superior efficacy of DMT in the earlier stages of MS[16]. Lastly, recent evidence points to a "window of opportunity" for achieving the highest effectiveness of DMT, which is open during the period of highest inflammatory activity — usually initiated by the first demyelinating attack.[31] Accordingly, it may be that more effective therapy early in the disease course improves long-term outcomes; which was the findings of this study. However, the balance of risk versus benefit of starting initial heDMT likely differs according to the individual patient, and a "one size fits all"-approach is probably not optimal. Firstly, the willingness to risk more frequent and more serious side effects to achieve a greater treatment effect varies from patient to patient – as well as between neurologists. Secondly, despite evidence and consensus regarding many prognostic variables in MS, an accurate and reliable method for predicting long-term outcomes in individual patients is yet to be established, which limits the ability to optimize treatment decisions in newly diagnosed patients.[32] The limited evidence on this subject is also evidenced by the discrepancies in current treatment guidelines, on the subject of initial heDMT in MS.[9,11]

The results of an observational study comparing initial heDMT with initial meDMT suggested a lower risk of a sustained EDSS worsening in patients starting heDMT as a first therapy, although the results did not reach statistical significance.[33] In the same study the authors found a difference in 5-year EDSS change of approximately 1 point between exposure groups, favoring initial heDMT. Also, two-thirds of patients initially receiving heDMT were treated with alemtuzumab, with the rest receiving natalizumab. In our study, most patients who started directly on heDMT received natalizumab (69.1%) or fingolimod (30.4%). Another discrepancy between the studies is the

classification of the efficacy of fingolimod. In accordance with the classification of treatments by EMA and the regulatory authorities in Denmark we defined fingolimod as a heDMT. Reclassifying the 61 patients treated with fingolimod to meDMT-treated patients in an exploratory analysis did not change the results.

A large observational study found a lower risk of conversion to secondary progressive MS (SPMS) in patients receiving initial treatment with fingolimod, alemtuzumab, or natalizumab, when compared to patients treated initially with glatiramer acetate or interferon-β.[34] For that study, the authors defined the endpoint of conversion to SPMS using a validated, objective, registry-based definition.[35] While the endpoint for that study differs from ours, both EDSS accumulation and the conversion to SPMS are associated with a higher disease activity early in the disease course[28–30], which can explain the beneficial effects of initial heDMT in both studies despite the difference in assessed endpoints.

Our study is an observational, non-randomized study and accordingly has inherent risks of unmeasured confounders. We were able to control for age, sex, disease duration, calendar year, pre-treatment relapse activity, and baseline EDSS score. In a sub-group of patients, we were also able to adjust for baseline T2 lesion load, which presumably is an important aspect in the treatment decisions of clinicians, and also being associated, although weakly, with long-term disease outcomes[36]. Our estimates proved comparable to the main analysis. A limitation is that only half of patients started on heDMT had a valid baseline MRI. This can negatively influence the generalizability of results, especially if patients with available baseline MRI are systematically different to patients without. However, as virtually all patients are given an MRI before treatment start in Denmark, missing values are probably due to a lack of data-entry by the clinician which, presumably, is random. We were not able to control for the severity of baseline relapses which must be assumed to influence the treatment decision of the clinician. The baseline characteristics of our

patients were in good accordance with previously published evidence on patients treated with initial heDMT, which suggests sufficient data quality and external validity[33,34].

Patients in the heDMT-group had a slightly higher density of EDSS scores during follow-up than the meDMT-initiators. Both theoretically and in our experience, a higher density of EDSS scores is usually associated with a higher probability of meeting the outcome of confirmed EDSS worsening. In this study, we saw a lower probability of meeting this outcome in the group with the highest EDSS score density, which may suggest that the true effect of interest may be even higher, although the magnitude is likely small since the differences were negligible.

Due to the availability of drugs, patients in the heDMT-group were generally initiated on therapy in later years compared to the meDMT-group. This is a potential cause of a "Will Rogers"-effect, which could contribute to better outcomes in patients initiating heDMT[37]. To limit this bias, we restricted our analysis to patients diagnosed after the first McDonald criteria were introduced. In Denmark, recent years have seen an increased use of initial heDMT in patients with poor prognosis as perceived by the clinician. A large part of this is based on MRI parameters, number, and severity of relapses leading up to diagnosis. As we had only information about the number of relapses and not about the severity of relapses and complete MRI parameters, exact matching on calendar year would likely increase the potential for unmeasured confounding. On the other hand, we did not see major differences in the estimates when limiting the analysis to patients starting treatment after 2006.

We did not have information on ethnicity of patients in our study. A lack thereof can prevent determination of generalizability to other settings. However, a recent study using the DMSR found that a high proportion of patients (>90%) registered were ethnically Danish[38]. If ethnicity is also potentially linked to disease outcomes, a skewed distribution of patient ethnicity across exposure-

groups could also induce confounding bias. While we cannot prove that groups were similar in this regard, we have no reason to suspect any systematic difference as access to DMT are provided free of charge and with equal structural access to every Danish inhabitant.

In conclusion, in this study assessing the effect of initial heDMT on disease outcomes, we observed a lower risk of 6-month confirmed EDSS worsening, and a lower risk of on-treatment relapses when comparing patients initiating heDMT as the first therapy with similar patients starting first time therapy with meDMT.

Acknowledgments

The authors would like to acknowledge the Danish MS Society for funding The Danish Multiple Sclerosis Registry and all MS clinics in Denmark for providing data to the Danish Multiple Sclerosis Registry.

The authors would like to acknowledge the Danish Multiple Sclerosis Society for assisting the Danish Multiple Sclerosis Registry.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Appendix 1

Name	Location	Role	Contribution
Mathias Buron, MD	Danish Multiple Sclerosis Center, Rigshospitalet, Denmark	Author	Designed and conceptualized the study, extracted and analyzed data, interpretation of results, wrote the manuscript.
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Tables

Table 1. Baseline characteristics.

	heDMT-group (n=194)	meDMT-group (n=194)
Female sex (%)	131 (67.5)	131 (67.5)
Mean age (SD)	35.1 (10.9)	35.2 (9.5)
Median follow-up years [IQR]	3.3 [2.1-4.6]	6.1 [3.3-9.8]
Median follow-up years, pairwise censoring [IQR]	2.63 [1.86-3.99]	2.63 [1.86-3.99]
Median follow-up years in patients starting DMT after 2006	3.3 [2.1-4.6]	5.3 [2.9-7.7]
Median calendar year [IQR]	2013 [2012-2015]	2009 [2005-2013]
Mean disease duration in years (SD)	4.1 (5.5)	4.7 (5.6)
Mean EDSS (SD)	2.7 (1.2)	2.6 (1.2)
Mean prior 24 months relapse count (SD)	2.2 (1.3)	2.3 (1.2)
Escalation of DMT (%)	-	75 (38.7)
Disease-modifying therapy (%)		
interferon-β	-	149 (76.7)
glatiramer acetate	-	17 (8.8)
teriflunomide	-	25 (12.9)
dimethyl fumarate	-	3 (1.6)
natalizumab	134 (69.1)	-
fingolimod	59 (30.4)	-
alemtuzumab	1 (0.5)	-

Table legend 1: SD=Standard deviation. IQR=Inter-quartile range; heDMT: highly effective disease-modifying therapies; meDMT: moderately effective disease-modifying therapies.

Figure titles and legends

Figure 1 title: Proportion of treatment-naïve patients starting heDMT according to calendar year.

Figure 1 legend: *DMT: disease-modifying therapy, heDMT: High efficacy DMT, meDMT: Moderate efficacy DMT.*

Figure 2 title: Patient inclusion flow-chart.

Figure 2 legend: *DMT: disease-modifying therapy, heDMT: High efficacy DMT, meDMT: Moderate efficacy DMT, EDSS: Expanded disability status scale.*

Figure 3 title: Probability of 6-month confirmed EDSS worsening. 1-Kaplan-Meier estimates

Figure 3 legend: *heDMT: High efficacy DMT, meDMT: Moderate efficacy DMT, EDSS: Expanded disability status scale. Opaque color indicates pointwise 95% confidence intervals.*

Figure 4 title: Probability of 6-month confirmed EDSS worsening. 1-Kaplan-Meier estimates. Pair-wise censoring.

Figure 4 legend: *heDMT: High efficacy DMT, meDMT: Moderate efficacy DMT, EDSS: Expanded disability status scale. Opaque color indicates pointwise 95% confidence intervals.*

Figure 5 title: Probability of a first relapse. 1-Kaplan-Meier estimates.

Figure 5 legend: *heDMT: High efficacy DMT, meDMT: Moderate efficacy DMT, EDSS: Expanded disability status scale. Opaque color indicates pointwise 95% confidence intervals.*