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ORIGINAL COMMUNICATION

Treatment escalation leads to fewer relapses compared with switching to another moderately effective therapy

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Abstract

Background Patients with multiple sclerosis who experience disease breakthrough often switch disease-modifying therapy (DMT).

Objective To compare treatment effectiveness of switch to highly effective DMT (heDMT) with switch to moderately effective DMT (meDMT) for patients who switch due to disease breakthrough defined as at least one relapse within 12 months of their treatment switch.

Methods We retrieved data from The Danish Multiple Sclerosis Registry on all relapsing-remitting MS patients with expanded disability status scale (EDSS) less than 6 who experienced disease breakthrough. We used propensity score matching to compare annualized relapse rates (ARRs), time to first confirmed relapse, time to first confirmed EDSS worsening and time to first confirmed EDSS improvement.

Results Each matched group comprised 404 patients. Median follow-up time was 3.2 years [interquartile range (IQR) 1.7–5.8]. ARRs were 0.22 (0.19–0.27) with heDMT and 0.32 (IQR 0.28–0.37) with meDMT; relapse rate ratio was 0.70 (95% CI 0.56–0.86; $p=0.001$). Escalation to heDMT reduced the hazard of reaching a first relapse (HR 0.65; 95% CI 0.53–0.80; $p<0.001$). We found no evidence of delayed disability worsening (HR 0.83; 95% CI 0.62–1.10; $p=0.20$) and weak evidence of disability improvement (HR 1.33; 95% CI 1.00–1.76; $p=0.05$) with heDMT.

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Conclusion Switching to heDMT is associated with reduced ARR and delay of first relapse compared with switching to meDMT. Patients on DMT who experience relapses should escalate therapy to heDMT.

Keywords Multiple sclerosis · Observational comparison study · Disease-modifying therapy · Treatment switch

Introduction

The disease course of multiple sclerosis (MS) is usually relapsing–remitting, with acute exacerbations followed by full or partial remission of symptoms. Incomplete remission of relapse symptoms can lead to long-lasting neurological deficits. In addition, the so-called silent lesions in the brain and spinal cord may cause permanent disability even in the absence of relapses. Several disease-modifying therapies (DMT) have been approved for the treatment of relapsing-remitting MS (RRMS) [1, 2]. The earliest approved therapies [interferon beta (INFβ) and glatiramer acetate (GA)] for RRMS reduced the relapse rate by approximately 30% compared with placebo [3–6], teriflunomide and dimethyl fumarate with 31–36% and 44–52%, respectively [7–10], whilst the highly effective therapies (heDMT) reduced relapse rates up to 68% compared with placebo [11–13]. Only fingolimod and alemtuzumab were compared with a moderately effective DMT (meDMT) in a randomized controlled setting as natalizumab was studied as an add-on therapy to INFβ [14–17]. However, the superior effect of these heDMTs may be associated with an increased risk of serious adverse events. In Denmark, the perceived unfavorable risk–benefit profiles of the currently approved heDMTs (also called second-line treatment: fingolimod, natalizumab, alemtuzumab, cladribine and ocrelizumab) are the reason for initiation of therapy with drugs that are only moderately effective (meDMT) but considered safer (also called first-line treatment: any INFβ product, GA, teriflunomide or dimethyl fumarate). HeDMTs are restricted as first choice for patients with a severe disease course at the time of diagnosis or as second choice in patients who experience disease breakthrough while on an meDMT.

A few early studies showed reduced relapse rates after switching to another meDMT in patients who switch due to disease breakthrough [18, 19], and this may be one of the reasons why patients with disease breakthrough on an meDMT are still occasionally switched to another meDMT instead of being escalated to an heDMT. In this study, we aimed at comparing relapse incidence, disability worsening and disability improvement in patients with RRMS who following disease breakthrough switched to another meDMT with patients who escalated treatment from an meDMT to an heDMT.

Method

Study design

The study is a population-based, prospectively recorded cohort study using the nationwide Danish Multiple

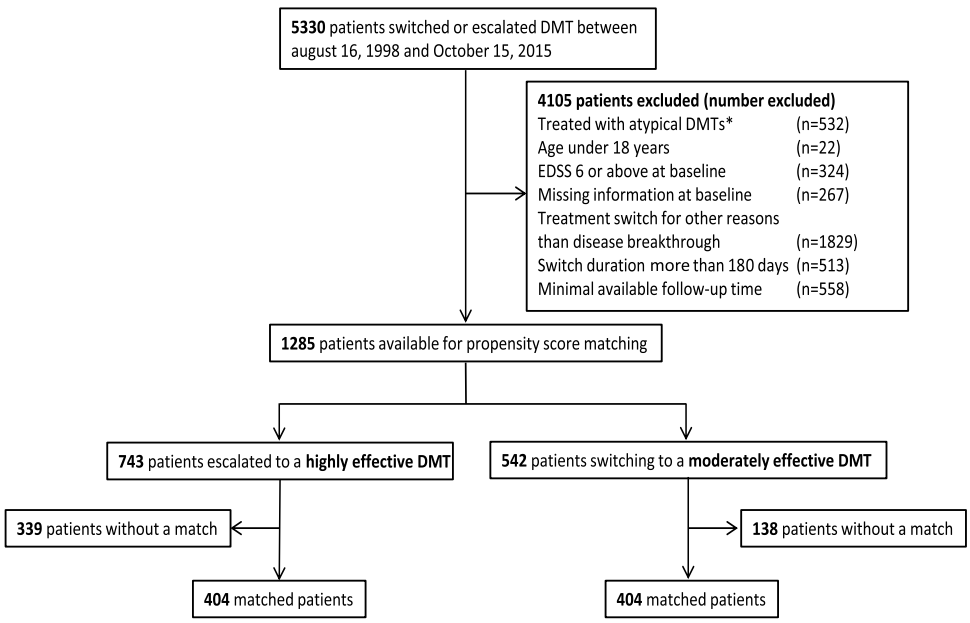


Fig. 1 Patient disposition chart. *DMTs that are not used as first-line drugs for patients with RRMS: Methotrexate (21), mitoxantrone (206), azathioprine (1), IVIG (43), Treosulphan (12), pulse methylprednisolone (19), rituximab (2), clinical trial DMT (1), other treatments/treatments not registered (186), natalizumab (35) and fingolimod (6). *DMT* disease-modifying therapy, *EDSS* expanded disability status scale

Sclerosis Registry (DMSR). The records in the DMSR include all patients treated with DMTs, as required by Danish regulators. Patients were included between August 16, 1998 (when all injectables were approved in Denmark) and October 21, 2015 (date of data extraction). Inclusion criteria were prior treatment with no more than one meDMT approved for treatment of RRMS and a subsequent disease breakthrough-induced treatment switch. Other criteria were 18 years of age or more at baseline, baseline EDSS below 6.0, no missing baseline data and a treatment discontinuation gap of less than 180 days (Fig. 1). The inclusion criterion disease breakthrough was defined as the occurrence of at least one relapse within 1 year of treatment switch or if the treating physician recorded the reason for switching therapy as "treatment failure". The cohort was divided in an meDMT group (switching from one meDMT to another) and an heDMT group (escalating from an meDMT to an heDMT). No patients in Denmark switched directly from their first prescribed meDMT to alemtuzumab. Patients switching to an off-label DMT (e.g., rituximab) and patients treated with an DMT associated with progressive MS (methotrexate, treosulphan and mitoxantrone) were excluded. Clinical visits without a corresponding EDSS record were also excluded. Start of follow-up was defined as the first day of treatment after changing therapy. Patients who did not reach an outcome were censored at switch between heDMT and meDMT, last recorded visit, death or date of data extraction, whichever occurred first. Within-class switches were not censored. All visits occurring with an interval longer than 3 years after the preceding visit were excluded (2.5% of visits).

Outcome measures

The primary outcome was annualized relapse rate (ARR) and was calculated as the average number of relapses per year during follow-up. The difference in ARR was expressed as relapse rate ratio comparing patients who escalated to an heDMT with patients who switched to an meDMT. Secondary outcomes were time to first relapse, time to first 3-month confirmed EDSS worsening, time to first 3-month confirmed EDSS improvement, time to recurrent relapses and time to recurrent EDSS worsening. An EDSS worsening was defined as a 1.5-point increase if baseline EDSS was 0; 1.0-point increase if baseline EDSS was between 1.0 and 5.5; and 0.5-point increase if baseline EDSS was more than 5.5.

Statistical analyses

We used propensity score matching to balance the two groups. Age at baseline, sex, prior DMT, EDSS at baseline, disease duration from onset to baseline and number of relapses 12 months prior to baseline were included as independent variables in the multivariable logistic regression model used to estimate the propensity scores. EDSS at baseline was classified into five categories (Table 2). All patients had an EDSS record in relation to their treatment start. Patients in the meDMT and heDMT groups were then matched in 1:1 ratio using the nearest neighbor procedure with a caliper of 0.01 and without replacement. The ARR in each study group was compared with a negative binomial regression model taking the paired structure of the data into account. We used Kaplan–Meier estimation to illustrate time from baseline to first relapse, time to first confirmed EDSS worsening and time to first confirmed EDSS improvement. Cox proportional hazards models were used to compare hazard rates for time to first relapse, time to first confirmed EDSS worsening and time to first confirmed EDSS improvement. We used an Andersen–Gill model to compare time to recurrent relapses and time to recurrent EDSS worsening. Proportional hazards were assessed in each model using cumulative martingale residuals. We did not consider death as a competing risk due to the small number of deaths during follow-up; instead, we handled these deaths as standard censorings. We conducted several sensitivity analyses to increase robustness of our results. We changed the caliper in the matching procedure to 0.1, changed the inclusion criteria to EDSS less than 4 at baseline and restricted the study population to patients with a recorded relapse within 6 months of baseline. Moreover, we repeated the analyses with heDMT defined as natalizumab or fingolimod, respectively.

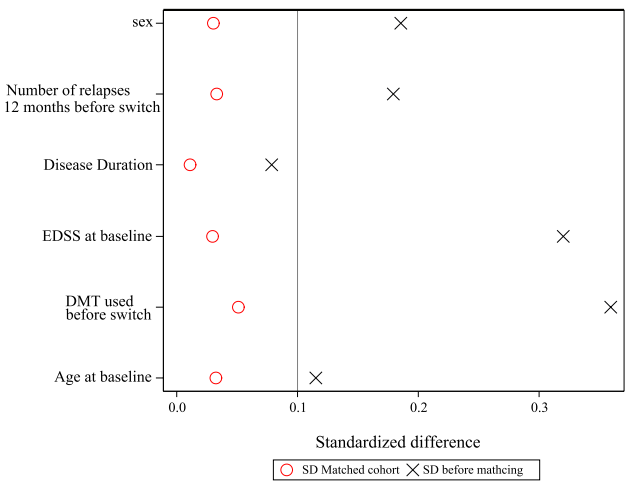
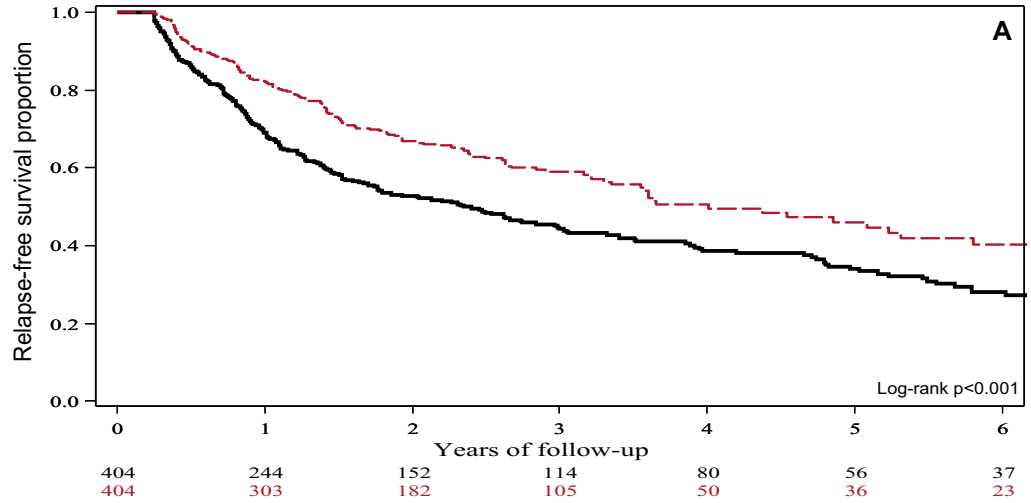
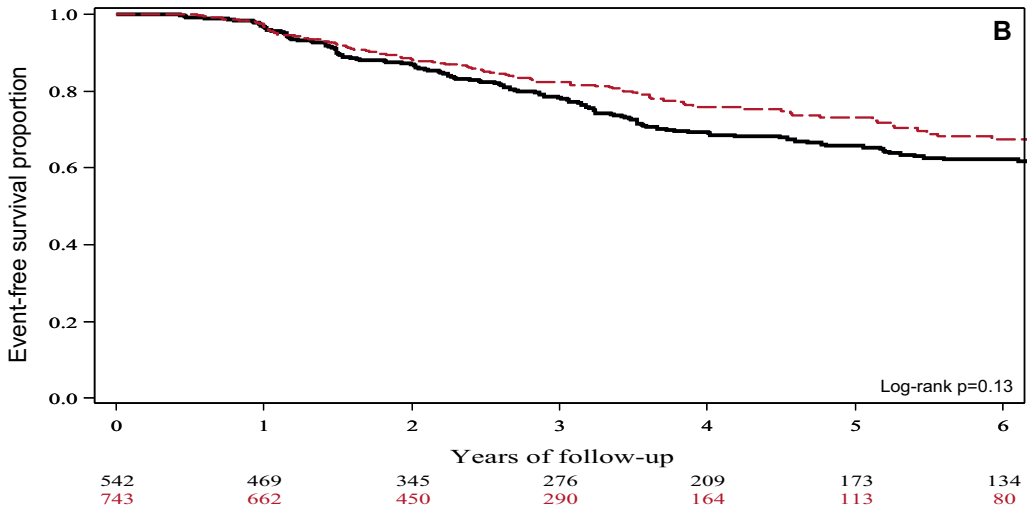
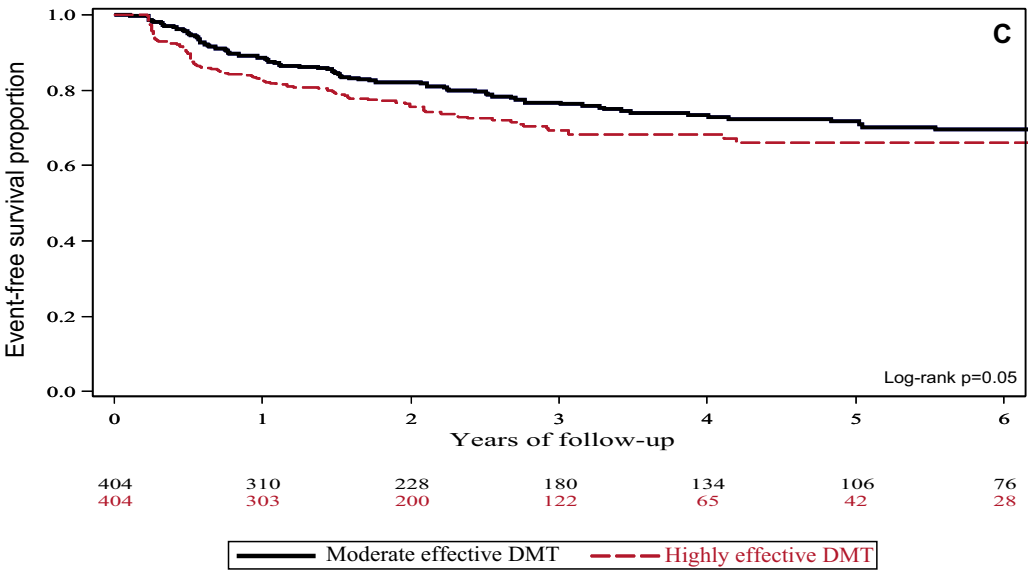


Fig. 2 Standardized differences before and after the propensity score procedure. *SD* standardized difference, *EDSS* expanded disability status scale, *DMT* disease modifying therapy


A
Relapse-free survival proportion
1.0
0.8
0.6
0.4
0.2
0.0
Log-rank p<0.001
0 1 2 3 4 5 6
Years of follow-up
404 244 152 114 80 56 37
404 303 182 105 50 36 23


B
Event-free survival proportion
1.0
0.8
0.6
0.4
0.2
0.0
Log-rank p=0.13
0 1 2 3 4 5 6
Years of follow-up
542 469 345 276 209 173 134
743 662 450 290 164 113 80


C
Event-free survival proportion
1.0
0.8
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0.2
0.0
Log-rank p=0.05
0 1 2 3 4 5 6
Years of follow-up
404 310 228 180 134 106 76
404 303 200 122 65 42 28
Moderate effective DMT
Highly effective DMT

◂**Fig. 3** Kaplan Meier curves of time to the first relapse (**a**), time to the first 3-month confirmed EDSS worsening (**b**) and time to the first 3-month confirmed EDSS improvement (**c**) comparing patients who escalated therapy to a highly effective disease-modifying treatment (heDMT) with patients who switched to another moderately effective disease-modifying therapy (meDMT)

Results

Of the patients, 743 escalated to an heDMT and 542 switched to an meDMT and were eligible for inclusion in the study (Fig. 1). Baseline demographic and clinical characteristics are shown in Table 1. High-level EDSS and male sex were the strongest predictors of switch to heDMT, while treatment with INFβ-1A 22 µg intramuscularly or INFβ-1B compared with other DMTs predicted switch to an meDMT. Output from the logistic regression is available in the appendix (supplemental Table 1) and the EDSS categories are shown in Table 2. After propensity score matching, the study population consisted of 404 patients in each group, further excluding 477 patients. Baseline variables used in the propensity score were well-balanced by the matching procedure, with all variables having a standardized difference less than 0.1 (Fig. 2). The majority of patients were included based on a registered relapse within 12 months prior to their treatment switch. Only 6.3% of patients were included exclusively as their switch was labeled as "treatment failure"—4.1% in the heDMT group and 2.2% in the meDMT group. Death was a rare reason for censoring with only six patients (0.7%) dying within one year from their last visit making death negligible as a competing risk. The median follow-up time was 3.2 years [interquartile range (IQR) 1.7–5.9]. Follow-up was comparable between groups: 3.1 years (IQR 1.7–5.9) and 3.3 years (IQR 1.6–6.0) for patients changing treatment to meDMT and heDMT, respectively. The mean number of visits per year during follow-up was also similar with 2.48 visits per year in the heDMT group and 2.52 visits per year in the meDMT group.

Primary and secondary outcomes

The post-switch ARR for patients escalating to an heDMT was 0.22 (95% CI 0.19–0.27), whereas the post-switch ARR for patients switching to another meDMT was 0.32 (95% CI 0.28–0.37), corresponding to a relative reduction of 30% [relapse rate ratio 0.70 (95% CI 0.56–0.86; $p=0.001$)]. As illustrated in the Kaplan–Meier curve, patients who escalated to an heDMT had a larger probability of remaining relapse-free compared with the group who switched to another meDMT (log-rank test $p<0.001$) (Fig. 3a). Patients who escalated to an heDMT showed a 35% reduced hazard rate of first relapse (HR 0.65; 95% CI 0.50–0.76; $p<0.001$), which was also seen in the Andersen–Gill analysis (HR 0.72; 95% CI 0.59–0.88; $p=0.001$). We found no clear evidence of a difference in EDSS worsening between the two groups (HR 0.83; 95% CI 0.62–1.10; $p=0.20$). This result was supported by the recurrent worsening analysis (HR 0.87; 95% CI 0.71–1.06; $p=0.16$). Lastly, we found a higher hazard rate of improvement in the group of patients who escalated to heDMT—with the estimate only just reaching statistical significance (HR 1.33; 1.00–1.76; $p=0.05$). Kaplan–Meier curves for time to first worsening and time to first improvement are seen in Fig. 3b, c. Log-rank tests for EDSS worsening and EDSS improvement were $p=0.13$ and 0.05, respectively. All results are shown in Table 3.

Sensitivity analyses

The results of the sensitivity analyses are shown in Table 4. First, we increased the caliper in the matching procedure to 0.1. This resulted in the larger matched sample of 836 patients. The results corroborated those of the primary analysis. The stricter criteria requiring EDSS less than 4.0 at baseline and relapse within 6 months of switching reduced the study sample. Again, the results of the primary analysis were confirmed. Finally, we stratified heDMT to either fingolimod or natalizumab. In both scenarios fingolimod and natalizumab were associated with superior control of relapse activity compared with the meDMT group, confirming the results of the primary analysis. It should be noted that the stratified analysis is not a comparison between fingolimod and natalizumab, as these two cohorts were not matched against each other. Accordingly, the low relapse rate ratio in the fingolimod analysis cannot be directly compared with the slightly higher relapse rate ratio from the natalizumab analysis.

Discussion

In this study, based on nationwide population-based registry data, we explored the effect of escalating therapy to an heDMT compared with switching to another meDMT in patients with RRMS who experienced disease breakthrough during treatment with an meDMT. The observed 28–35% relative reduction in relapse activity is of the same magnitude as the effect of meDMTs compared with placebo. On average, patients experienced 0.22 relapses per year on heDMT and 0.32 relapses per year on meDMT. Therapy escalation to heDMT was associated with increased time free of relapses compared with a switch to meDMT. The difference in hazard rate of 3-month confirmed EDSS worsening did not reach statistical significance, while the 3-month confirmed EDSS improvement analysis only just reached this threshold. The probability of switching between meDMTs was higher for patients originally treated with INFβ-1A

Table 1 Baseline demographic and clinical characteristics of the matched groups treated with moderately effective therapies (heDMT) or highly effective therapies (heDMT)

Median (IQR)	meDMT group	heDMT group
No. of patients	404	404
Mean age (SD), years	39.2 (9.6)	39.4 (9.2)
Sex, female (%)	70.0	71.0
EDSS	2.5 (2.0–3.5)	2.0 (2.0–3.5)
No of relapses 12 months before baseline	1 (1–2)	1 (1–2)
Disease duration, years	5 (3–10)	5 (3–10)
Calendar year at treatment switch	2008 (2004–2010)	2012 (2010–2013)
Duration of treatment gap, days	1 (0–14.5)	5.5 (0–29)
DMT, switching from		
Interferon beta-1a 30 µg IM	51.9%	49.2%
Interferon beta-1b 250 µg SC	12.8%	13.9%
Interferon beta-1a 22 µg SC	17.3%	17.8%
Interferon beta-1a 44 µg SC	12.3%	13.1%
Glatiramer acetate	5.1%	6.1%
Teriflunomide	0.2%	0.2%
DMT, switching to		
Interferon beta-1a 30 µg IM	11.8%	
Interferon beta-1b 250 µg SC	4.2%	
Interferon beta-1a 22 µg SC	18.3%	
Interferon beta-1a 44 µg SC	14.3%	
Peginterferon beta-1a 125 µg SC	0.2%	
Glatiramer acetate	35.3%	
Teriflunomide	3.7%	
Dimethyl fumarate	10.1%	
Natalizumab		57.2%
Fingolimod		42.8%

IM intramuscularly, *SC* subcutaneously, *µg*: microgram, *IQR* interquartile range, *SD* standard deviation, *EDSS* expanded disability status scale

Table 2 EDSS level categorized for logistic regression

EDSS category 0	EDSS = 0
EDSS category 1	EDSS = 1.0–2.5
EDSS category 2	EDSS = 3.0–3.5
EDSS category 3	EDSS = 4.0–4.5
EDSS category 4	EDSS = 5.0–5.5

EDSS expanded disability status scale

22 µg intramuscularly or INFβ-1B. This could be explained by the higher probability of developing neutralizing antibodies on INFβ-1B treatment [20, 21], and because it was possible to switch to the higher dose of INFβ-1A (22 µg intramuscularly to 44 µg intramuscularly).

Treatment strategies have become more complex over the years with the approval of several DMTs. When natalizumab became available, the option of a more effective therapy appeared. Even though fingolimod and natalizumab were shown to be more effective than IFNβ in the randomized controlled trials [11, 13, 15, 22], they are used only as first-line therapy in patients with high disease activity at diagnosis [23] and as second-line therapy in patients treated with so-called first-line therapies who experience disease breakthrough. However, not all patients are escalated to an heDMT when experiencing disease breakthrough. In some countries, local regulations, regional availability of DMTs and reimbursement restrictions may be responsible for this, but even in countries with unrestricted drug availability, not all patients with disease breakthrough are escalated to an heDMT. A few small studies have reported that switching from one meDMT to another reduced ARR [18, 19, 24]. One study [18] showed a large decline in ARR from 1.23 to 0.53 in patients who switched due to clinical disease activity. This group of patients was not compared with a control group, suggesting that the large reduction in ARR probably represents the combined effect of treatment switch and regression to the mean. The two other studies showed ARRs between 0 and 0.25 after switching from one meDMT to another. A comparative study [25] found that patients with on-treatment clinical disease activity who switched to INFβ or GA had more relapses than those who escalated to

Table 3 Primary and secondary outcomes in patients who after disease breakthrough on a moderately effective disease-modifying treatment (meDMT) escalated therapy to a highly effective disease-modifying treatment (heDMT) and patients who switched to another meDMT

Treatment group	heDMT	meDMT
No. of matched patients	404	404
Primary outcome, rate (95% CI)		
Annualized relapse rate	0.22 (0.19–0.27)	0.32 (0.28–0.37)
Relapse rate ratio	0.70 (0.56–0.86; $p=0.001$)	
Secondary outcomes, HR (95% CI)		
Hazard ratio of first relapse	0.65 (0.53–0.80; $p<0.001$)	
Hazard ratio of recurrent relapses	0.72 (0.59–0.88; $p=0.001$)	
Hazard ratio of first worsening	0.83 (0.62–1.10; $p=0.20$)	
Hazard ratio of recurrent worsening	0.87 (0.71–1.06; $p=0.16$)	
Hazard ratio of first improvement	1.33 (1.00–1.76; $p=0.05$)	

HR hazard ratio, *CI* confidence interval, *meDMT* moderately effective disease-modifying therapy, *heDMT* highly effective disease-modifying therapy

fingolimod. Post-switch ARRs were 0.42 and 0.31 for the INFβ/GA treated group and the fingolimod treated group, respectively. Moreover, the HRs for first relapse and first disability worsening were 0.74 (95% CI 0.56–0.98) and 0.53 (95% CI 0.31–0.91) favoring fingolimod. A similar register-based study [26] compared patients who switched from a first-line therapy to another first-line therapy with a group of patients who switched to natalizumab. The natalizumab-treated group did markedly better with an ARR of 0.20 compared with 0.58 in the control group. In addition, patients treated with natalizumab showed a reduced hazard rate of 3-month confirmed disability worsening (HR 0.74; 95% CI 0.55–0.74). Data from the Danish Multiple Sclerosis Registry have earlier been used to compare switching from a first-line therapy to either natalizumab or fingolimod. ARRs in this study were 0.296 and 0.307 for natalizumab and fingolimod, respectively [27]. Other studies have also investigated this issue [28, 29]. We did not show a statistically significant treatment effect in preventing disability worsening as was shown in the two mentioned comparison studies [25, 26]. Differences in study design and source population may explain the conflicting results. We included patients who had been treated with no more than one DMT before their therapy switch, resulting in inclusion of patients early in their disease course. It is well-known that worsening in EDSS in patients who are early in the disease course is relatively infrequent, irrespective of the treatment. Moreover, the comparative groups in our study were differently defined compared with the other studies as we included all INFβ, GA, teriflunomide and dimethyl fumarate in the meDMT group.

The ideal timepoint during a patient's disease course to start treatment with an DMT, to switch DMT or to stop DMT is difficult to predict [30]. A systematic review concluded that an early start of high-efficacy therapies has more potential in suppressing relapse activity [31]. It is important to escalate treatment in patients where switch to a more aggressive treatment will provide better disease control, but it is also important to avoid overtreating patients. The definition of disease breakthrough necessary for escalation has changed over time. Today, radiological disease breakthrough, defined as new lesions, newly enlarged lesions or GAD-enhancing T2 lesions, fulfill the criterion for escalation [32]. The strategy of switching due to MRI changes has evolved despite all pivotal RCTs required at least one clinical relapse within 12 months of start of follow-up. Accordingly, the guidelines recommending escalation to an heDMTs due to MRI worsening alone are not supported by strong evidence; nevertheless, escalation is still recommended in the ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis [32] and has become common practice. We defined disease breakthrough as the occurrence of a relapse within 12 months of the treatment switch constituting a modest disease activity. Despite this, we found a convincing effect on all relapse-related outcomes. Supportive of these results are the result of the sensitivity analysis requiring at least one relapse within 6 months of the treatment switch which also was convincing.

The limitations of our study are the potential bias due to unmeasured confounders, MRI data being the primary concern. However, data were collected in daily clinical practice and until recently only clinical disease breakthrough allowed escalation to heDMT. Another limitation is that the reason for switching versus escalating DMT could be systematically different in a way not captured by the propensity score. This risk was mitigated by the criterion that all patients experienced disease activity within 12 months of the change of DMT. Moreover, we tested whether requiring disease activity within 6 months of the change of DMT would change the study results. The results from these two analyses were

Table 4 Sensitivity analyses in patients who after disease breakthrough on a moderately effective disease-modifying treatment (meDMT) escalated therapy to a highly effective disease-modifying treatment (heDMT) and patients who switched to another meDMT

	Annualized relapse rate	Relapse rate ratio	First relapse HR (95% CI)	First worsening HR (95% CI)	First improvement HR (95% CI)
Sensitivity analyses					
Main results (404 matches)	heDMT: 0.22 (0.19–0.27) meDMT: 0.32 (0.28–0.37)	0.70 (0.56–0.86) $p = 0.001$	0.65 (0.53–0.80) $p<0.001$	0.83 (0.62–1.10) $p = 0.20$	1.33 (1.00–1.76) $p = 0.05$
Increase matching caliper to 0.1 (418 matches)	heDMT: 0.23 (0.20–0.27) meDMT: 0.32 (0.28–0.36)	0.73 (0.60–0.90) $p = 0.003$	0.70 (0.58–0.85) $p < 0.001$	0.84 (0.63–1.13) $p = 0.25$	1.29 (0.98–1.70) $p = 0.07$
Relapse within 180 days instead of 365 days (309 matches)	heDMT: 0.25 (0.21–0.29) meDMT: 0.36 (0.32–0.42)	0.68 (0.54–0.84) $p < 0.001$	0.59 (0.47–0.74) $p < 0.001$	0.86 (0.63–1.18) $p = 0.34$	1.35 (1.00–1.84) $p = 0.05$
EDSS less than 4 at baseline (358 matches)	heDMT: 0.22 (0.18–0.26) meDMT: 0.31 (0.27–0.35)	0.71 (0.56–0.89) $p = 0.003$	0.68 (0.54–0.85) $p < 0.001$	0.98 (0.72–1.35) $p = 0.92$	1.65 (1.21–2.26) $p = 0.002$
heDMT=natalizumab (316 matches)	heDMT: 0.26 (0.22–0.30) meDMT: 0.35 (0.31–0.41)	0.72 (0.58–0.89) $p = 0.002$	0.76 (0.62–0.94) $p = 0.01$	0.80 (0.58–1.12) $p = 0.19$	1.31 (0.97–1.76) $p = 0.08$
heDMT=fingolimod (265 matches)	heDMT: 0.15 (0.12–0.21) meDMT: 0.31 (0.26–0.36)	0.50 (0.36–0.70) $p < 0.001$	0.48 (0.36–0.64) $p < 0.001$	0.82 (0.53–1.27) $p = 0.38$	1.27 (0.88–1.82) $p = 0.19$

HR hazard ratio, *CI* confidence interval, *heDMT* highly effective disease-modifying therapy, *meDMT* moderately effective disease-modifying therapy, *EDSS* expanded disability status scale

similar, indicating that the 12-month definition in the main analyses was robust. In addition, if patients switched from one meDMT to another for reasons other than disease breakthrough and were misclassified and included in the meDMT group, bias would be expected to be towards less disease activity in the meDMT group. The main strength of our study is it being nationwide and population-based and that DMT is prescribed in only 14 public MS clinics. Selection bias in the source population is almost non-existent as DMT is free of charge, and the regulatory authorities require that data from all patients with MS treated with an DMT are prospectively registered in the Danish MS registry. This also improves the generalizability of our results. In addition, we conducted multiple sensitivity analyses supporting the main results.

In conclusion, our results support international treatment guidelines recommending escalation to heDMT in patients who experience disease breakthrough on a meDMT. Further, we agree with the recommendation that treatment with the entire spectrum of DMTs should be implemented in centers with adequate infrastructure to provide proper monitoring of patients and prompt and correct response to disease breakthrough.

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Compliance with ethical standards

Conflicts of interest TC has received support for congress participation from Merck, Novartis, Biogen and Roche. TK served on scientific advisory boards for Roche, Genzyme-Sanofi, Novartis, Merck and Biogen, steering committee for Brain Atrophy Initiative by Genzyme, received conference travel support and/or speaker honoraria from WebMD Global, Novartis, Biogen, Genzyme-Sanofi, Teva, BioCSL and Merck and received research support from Biogen. BL has nothing to disclose. PS 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. MM has served on scientific advisory board for Biogen Idec, Novartis, Merck, Sanofi and Teva; has received honoraria for lecturing from Biogen Idec, Merck, Novartis and Genzyme; has received support for congress participation from Biogen Idec, Novartis, Genzyme and Teva.

References

1. Sorensen PS, Blinkenberg M (2016) The potential role for ocrelizumab in the treatment of multiple sclerosis: current evidence and future prospects. Ther Adv Neurol Disord 9:44–52
2. Sorensen PS (2014) New management algorithms in multiple sclerosis. Curr Opin Neurol 27:246–259
3. The IFNB Multiple Sclerosis Study Group (1993) Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. The IFNB Multiple Sclerosis Study Group. Neurology 43:655–661
4. Johnson KP, Brooks BR, Cohen JA (1995) Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind, placebo-controlled trial. Neurology 45:1268–1276
5. Jacobs LD, Cookfair DL, Rudick RA et al (1996) Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). Ann Neurol 39:285–294
6. Group P (1998) (Prevention of R and D by I β-1a S in MSS. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group. Lancet 352:1498–1504
7. O'Connor P, Wolinsky JS, Confavreux C et al (2011) Randomized trial of oral teriflunomide for relapsing multiple sclerosis. N Engl J Med 365:1293–1303
8. Confavreux C, O'Connor P, Comi G et al (2014) Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol 13:247–256
9. Fox RJ, Miller DH, Phillips JT et al (2012) Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N Engl J Med 367:1087–1097
10. Bar-Or A, Gold R, Kappos L et al (2013) Clinical efficacy of BG-12 (dimethyl fumarate) in patients with relapsing-remitting multiple sclerosis: Subgroup analyses of the DEFINE study. J Neurol 260:2297–2305
11. Polman CH, O'Connor PW, Havrdova E et al (2006) A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med 354:899–910
12. Calabresi PA, Radue E-W, Goodin D et al (2014) Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Neurol 13:545–556
13. Kappos L, Radue E-W, O'Connor P et al (2010) A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med 362:387–401
14. Radue EW, Stuart WH, Calabresi PA et al (2010) Natalizumab plus interferon beta-1a reduces lesion formation in relapsing multiple sclerosis. J Neurol Sci 292:28–35
15. Cohen JA, Barkhof F, Comi G et al (2010) Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med 362:402–415
16. Cohen JA, Coles AJ, Arnold DL et al (2012) Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet 380:1819–1828
17. Coles AJ, Twyman CL, Arnold DL et al (2012) Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet 380:1829–1839
18. Caon C, Din M, Ching W et al (2006) Clinical course after change of immunomodulating therapy in relapsing—remitting multiple sclerosis. Eur J Neurol 13:471–474
19. Gajofatto A, Bacchetti P, Grimes B et al (2009) Switching first-line disease-modifying therapy after failure: impact on the course of relapsing-remitting multiple sclerosis. Mult Scler 15:50–58
20. Vartanian TK, Zamvil SS, Fox E et al. Neutralizing antibodies to disease-modifying agents in the treatment of multiple sclerosis. Neurology 63:S42–S49
21. Koch-Henriksen N, Sorensen PS, Bendtzen K et al (2009) The clinical effect of neutralizing antibodies against interferon-beta is independent of the type of interferon-beta used for patients with relapsing-remitting multiple sclerosis. Mult Scler 15:601–605
22. Rudick RA, Stuart WH, Calabresi PA et al (2006) Natalizumab plus interferon Beta-1a for relapsing multiple sclerosis. N Engl J Med 354:911–923
23. Soelberg Sorensen P (2016) Safety concerns and risk management of multiple sclerosis therapies. Acta Neurol Scand. https://doi.org/10.1111/ane.12712 **(Epub ahead of print)**
24. Carrá A, Onaha P, Luetic G et al (2008) Therapeutic outcome 3 years after switching of immunomodulatory therapies in patients with relapsing-remitting multiple sclerosis in Argentina. Eur J Neurol 15:386–393
25. He A, Spelman T, Jokubaitis V et al (2015) Comparison of switch to fingolimod or interferon beta/glatiramer acetate in active multiple sclerosis. JAMA Neurol 72:405–413
26. Spelman T, Kalincik T, Zhang A et al (2015) Comparative efficacy of switching to natalizumab in active multiple sclerosis. Ann Clin Transl Neurol 2:373–387
27. Koch-Henriksen N, Magyari M, Sellebjerg F et al (2017) A comparison of multiple sclerosis clinical disease activity between

patients treated with natalizumab and fingolimod. Mult Scler J 23:234–241
28. Braune S, Lang M, Bergmann A (2016) Efficacy of fingolimod is superior to injectable disease modifying therapies in second-line therapy of relapsing remitting multiple sclerosis. J Neurol 263:327–333
29. D'Amico E, Leone C, Zanghì A et al (2016) Lateral and escalation therapy in relapsing-remitting multiple sclerosis: a comparative study. J Neurol 263:1802–1809
30. Gajofatto A, Benedetti MD (2015) Treatment strategies for multiple sclerosis: When to start, when to change, when to stop? World J Clin Cases 3:545–556
31. Merkel B, Butzkueven H, Traboulsee AL et al (2017) Timing of high-efficacy therapy in relapsing-remitting multiple sclerosis: a systematic review. Autoimmun Rev 16:658–665
32. Montalban X, Gold R, Thompson AJ et al (2018) ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis. Eur J Neurol 24:1–23