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Age and sex as determinants of treatment decisions in patients with relapsing-remitting MS

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ABSTRACT

Background: . Most patients with relapsing-remitting multiple sclerosis (RRMS) are initially treated with moderate efficacy disease-modifying therapies (meDMTs), and only a smaller group of highly active patients are initiated on a high efficacy disease-modifying therapy (heDMT). Real-world data have shown that choosing a heDMT as the initial therapy in highly active RRMS patients is more effective than using a meDMT, and that in patients with breakthrough disease on a meDMT escalation of treatment to a heDMT is more effective than staying on the same or switching to another meDMT. The role of age and sex as determinants for selection of the initial treatment intensity, and for using escalation of treatment intensity in patients with relapse activity on treatment with meDMTs, is only partially known.

Methods: . We included all Danish patients with RRMS registered in The Danish Multiple Sclerosis Registry who began a DMT since 2014 and stratified the cohort according to sex and age < 40 and ≥ 40 years at first DMT treatment. We studied determinants, with emphasis on age and sex, for the primary choice of therapy, for adherence to the initial therapy and for treatment escalation. Based on existing literature and clinical relevance, we included the following potential confounders in the analyses: DMT efficacy, pre-treatment relapse activity, disease duration, Expanded Disability Status Scale (EDSS) score, and, in a subgroup, MRI activity.

Results: . With all covariates mutually adjusted, patient age was a strong decisive factor for choosing a heDMT with odds ratio 1.69 for starting a heDMT in patients < 40 years compared with patients ≥ 40 years. Men had odds ratio 1.53 for starting with a heDMT compared with women. The odds ratio of heDMT in patients with EDSS > 3 vs ≤ 3 was 3.49, and every additional relapse was associated with increased odds ratio 2.33 for heDMT. Patients were more adherent to the initial heDMTs than to the initial meDMTs. Patients above 40 years were more prone to stay on the initial treatment compared to patients below 40, regardless of whether the initial treatment was meDMT ($p<0.001$) or heDMT ($p=0.008$) (covariates mutually adjusted). Relapse activity resulted in escalation of therapy to a heDMT in 67% of patients aged < 40 years ($N=273$) and in 56% patients aged 40 years or above ($N=159$) ($p=0.008$), and younger patients had odds ratio 1.46 of escalating therapy compared to older patients. Male patients were more likely to have treatment escalation to heDMTs than female patients (odds ratio 2.03).

Conclusion: . Age and sex appear to be independent determinants for the choice of the initial DMT and for the decision of treatment escalation in patients with breakthrough disease on a meDMT. It is unfortunate, if older age is a factor that make choice of a heDMT more unlikely, as many DMTs seems to be less efficacious in older patients.

1. Introduction

In Denmark, like in most other western countries, the majority of relapsing-remitting multiple sclerosis (RRMS) patients are initially treated with moderate efficacy disease-modifying therapies (meDMTs), in Europe termed first-line therapies, and only a smaller group of highly

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active patients are started on a high efficacy disease-modifying therapy (heDMT), in Europe termed second-line therapies, as the first choice (Comi et al., 2017; Sorensen, 2014).

The meDMTs include injectable platform therapies (interferon-beta 1a sc., interferon-beta 1a im., interferon-beta 1b, peginterferon-beta 1a and glatiramer acetate), teriflunomide and dimethyl fumarate. The approved heDMTs comprise natalizumab, fingolimod, ozanimod, alemtuzumab, cladribine, ocrelizumab and ofatumumab. In Denmark, a few patients have been treated with rituximab, mitoxantrone and experimental therapies.

Since the heDMTs natalizumab (2006) and fingolimod (2011) became available, patients with a suboptimal treatment response to a meDMT are offered treatment escalation to a heDMT, while patients with adverse effects and tolerability problems are usually changed to another meDMT (Comi et al., 2017; Sorensen, 2014).

Real-world data have shown that in patients with breakthrough disease on a meDMT escalation of treatment to a heDMT is more effective than switching to another meDMT (Chalmer et al., 2019), and that choosing a heDMT as the initial therapy in highly active RRMS patients is more effective than using a meDMT from the onset (Buron et al., 2020).

Whereas disease activity in the years prior to treatment start, EDSS and possibly disease duration are clinical characteristics that would be major determinants for starting a heDMT, age and sex *per se* would not be considered independent factors significantly involved in the choice of initial treatment intensity.

In this article, we have focused on patients who started their first DMT after January 1st, 2014 when the oral meDMTs teriflunomide and dimethyl fumarate had been approved in Denmark and the heDMTs natalizumab and fingolimod were available. We analyzed the determinants, particularly age and sex, for selection of treatment intensity of the initial therapy and escalation of treatment intensity in patients with relapse activity on treatment with meDMTs.

2. Patients and methods

2.1. Study population

We conducted a register-based cohort study based on data from The Danish Multiple Sclerosis Registry (DMSR) (Koch-Henriksen et al., 2015; Magyari et al., 2020). The DMSR was established in 1956 as an incidence and prevalence registry and has ever since collected data on all patients with MS in Denmark. Since 1996, it has been mandatory for all neurological departments in Denmark to regularly report real-time clinical data on all patients with MS receiving DMT in a standardised way, ensuring a high data completeness (Koch-Henriksen and Sorensen, 2000; Magyari et al., 2016). DMT is free of charge to all Danish residents and can only be prescribed and dispensed at specialised MS clinics in public hospitals, and real-time clinical information is entered into the online data collection platform at every clinical visit.

For our primary analyses, we included patients starting their first DMT after January 1st, 2014 and who started their first treatment within 6 months from data collection. Patients below 18 years of age at first treatment initiation were excluded. We investigated primary choice of therapy, adherence to the initial therapy and treatment escalation according to age at first DMT treatment. We dichotomised the primary choice of therapy into meDMT, i.e. interferons, glatiramer acetate, teriflunomide and dimethyl fumarate, and heDMT, i.e. natalizumab, fingolimod, alemtuzumab, cladribine and ocrelizumab. We examined treatment escalation among patients starting on a meDMT who experienced a relapse on their initial treatment (that is, 3 months after start until 3 months after treatment stop). Patients were followed to date of data collection (November 2, 2020), death or emigration, whichever came first. In a sub-cohort, we investigated the association between primary choice of treatment and age and sex among patients with an MRI record +/- 180 days from treatment start.

2.2. Covariates

Our exposure variables were sex (categorical: male and female) and age at first treatment start (categorical: age <40 years and ≥40 years) and the following potential confounders were included in the analyses: DMT efficacy (categorical: meDMT and heDMT), 24-month pre-therapy relapse activity (numerical), disease duration (numerical, per year increment, calculated as time from onset to first treatment start) and EDSS (Kurtzke, 1983) at baseline (+/- 6 months from treatments start, categorical: ≤3 and >3). We chose the potential confounders based on existing literature and clinical relevance.

2.3. Statistical analyses

The first DMT and the treatment courses are presented as frequencies with corresponding percentages. Comparisons between treatment groups according to sex and age at first treatment start was done based on Chi-square test.

Missing values occurred for EDSS (8%) and 24-month pre-therapy relapse activity (16%) for the cohort of patients starting on their first treatment after January 1st, 2014. We therefore performed multiple imputation to account for potential bias if the association was different for patients with and without missing data (White and Carlin, 2010). We assumed our data were missing at random. We used multistage PROC MI by Fully Conditional Specification to create 100 datasets with imputed missing values. Supplementary analyses based on complete data analysis were also performed. All covariates from the fully adjusted models were included in the imputation models. We used univariate and multivariate unconditional logistic regression to investigate the association between age (<40 vs ≥40 years) or sex (male vs female) and outcomes (efficacy and treatment escalation). We then combined the estimates from the 100 imputed datasets and calculated odds ratios with 95% confidence intervals (CI) and *p*-values based on Rubin's rule (Rubin, 1987). Subgroup analysis on patients with full information on MRI was based on complete-case analysis, and thus, no multiple imputation was performed on this sub-group. We also re-analysed all models as complete-case analysis to assess potential bias. Finally, we investigated interactions between covariates to assess effect modification.

All analyses were conducted using SAS version 9.4.

3. Results

3.1. Treatment initiation

Among 3,497 patients aged 18 years or above who started their first DMT after January 1st, 2014 and with at least 6 months of follow-up,

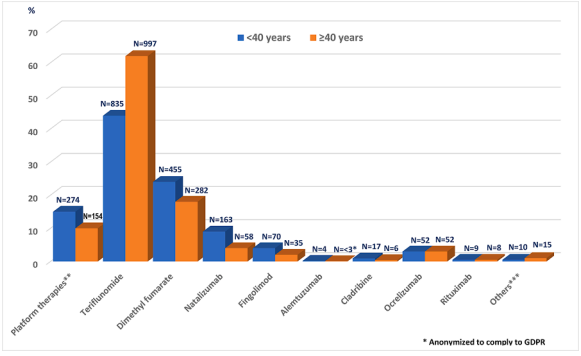

Fig. 1. Primary choice of therapy in patients (*N*=3,497) stratified according to age <40 (*N*=1,889) or ≥40 (*N*= 1,608) years. **Platform therapies: Interferon-beta preparations including peginterferon-beta 1a and glatiramer acetate; *** Other treatments: Daclizumab, mitoxantrone, non-approved experimental drugs.

1,889 patients were aged < 40 years, while 1,608 patients were 40 years or older. The primary choice of therapy appears from Fig. 1. Only 428 patients (12 %) initiated an injectable platform therapy, while the majority, 2,569 patients (73 %), were treated with an oral meDMT (teriflunomide or dimethyl fumarate). Overall, 1,564 (83 %) out of 1,889 patients < 40 years started on a meDMT while 306 (16 %) initiated a heDMT, compared to 1,433 out of 1,608 (89 %) patients ≥ 40 years starting on a meDMT and 152 (9 %) a heDMT.

The patient demographics and disease characteristics of appear from Table 1. Patient < 40 years had a lower EDSS, more relapses in the 24 months prior to treatment start, and less MRI burden than patients ≥ 40 years.

Patient age was a strong factor decisive for choosing a heDMT: the odds ratio for starting a heDMT in patients < 40 years was 1.69 compared with patients ≥ 40 years (Table 2 and Table e-1). Equally, sex was associated with selection of therapy; men had significantly higher odds (odds ratios 1.53) for starting with a heDMT compared with women. As expected, EDSS and 24 months pre-baseline relapse activity at treatment start were strongly associated with the choice of therapy so that higher EDSS was associated with increased odds of heDMT (odds ratio EDSS > 3 vs ≤ 3: 3.49), and every additional relapse was associated with increased odds of heDMT (odds ratios 2.33). Disease duration was inversely associated with the choice of DMT (odds ratio per year increment: 0.95) (Table 2 and Table e-1).

MRI data was only routinely reported to the registry during the most recent years and, hence, the group of patients with baseline MRI recorded within +/- 180 days from their first treatment start date who also had full information on relapses and EDSS score amounted to 1,741 patients. The number of baseline MRI T2-weighted lesions was also a strong predictor of receiving heDMT as the initial therapy. When patients were dichotomized according to number of baseline MRI T2-weighted lesions < 10 lesions and ≥ 10 lesions the fully adjusted odds ratio of starting a heDMT was 2.10 (95 % CI 1.50-2.93) for patients with ≥ 10 lesions (Table 3). The impact of age < 40 years versus ≥ 40 years did not change when including MRI lesions; the probability of having initial heDMT was 1.68 (CI 1.25-2.27). The effect of sex in this subcohort was slightly reduced with borderline significance with increased odds of receiving a heDMT among males.

When baseline brain MRI was dichotomized according to number of baseline MRI T2-weighted lesions < 5 lesions and ≥ 5 lesions the results was in the same order of magnitude (odds ratios: age 1.67; sex 1.32; disease duration 0.97; EDSS 3.10; 24 months pre-baseline relapse activity 2.57; MRI 2.33).

Table e-2 shows the effect of age (<40 vs ≥40) and sex (male vs female) on the probability of starting with a heDMT compared to a meDMT in the subgroup of patients who had a baseline MRI (*N*=1,741).

Table 1
Patient characteristics in patients (*N*=3,497) who started their first disease modifying therapy after 1.1.2014 stratified according to age <40 (*N*=1,889) or ≥40 (*N*= 1,608) years.

	<40 years old Mean (median, interquartile range)	≥40 years old Mean (median, interquartile range)
Sex: men/women, n (%)	598 (32)/1291 (68)	508 (32)/1100 (68)
Age at disease onset	28 (28, 23-33)	43 (43, 38-48)
Age at diagnosis	30 (30, 25-35)	47 (46, 42-51)
Age at treatment start	30 (30, 26-36)	49 (47, 44-52)
EDSS at treatment start*	1.8 (2.0, 1.0-2.5)	2.3 (2.0, 1.5-3.0)
Relapses in 24 months prior to treatment**	1.5 (1, 1-2)	1.4 (1, 1-2)
Number with ≥10 T2 lesions at treatment start***, n (%)	741 (65)	638 (72)

* Patients with missing values on EDSS, N=280;
** Patients with missing values on relapses, N=384; ***Patients with missing values on MRI, N=1473.

Table 2
Probability of starting with a high efficacy DMT compared to a moderate efficacy DMT in patients who started their first disease modifying therapy after 1.1.2014. Analyses based on multiple imputation analysis. All covariates are mutually adjusted (*N*=3,455).

Covariate	Odds ratio (95% CI)
Age <40 vs ≥40	1.69 (1.34-2.13)
Sex, male vs female	1.53 (1.23-1.90)
Disease duration, numerical, per year increment	0.95 (0.93-0.98)
24 months pre-baseline relapse activity, numerical, per additional relapse	2.33 (2.04-2.66)
EDSS score, categorical, ≥3 vs <3	3.49 (2.66-4.56)

Patients treated with rituximab or "other" DMTs are excluded from this analysis (n=42). EDSS: Expanded disability status scale.

Table 3
Probability of starting with a high efficacy DMT compared to a moderate efficacy DMT among subgroup of patients who started their first disease modifying therapy after 1.1.2014 and who had full information on MRI, EDSS and 24 months pre-baseline relapse activity at treatment start. Complete-case analysis. All covariates are mutually adjusted (*N*=1,741).

Covariate	Odds ratio (95% CI)
Age <40 vs ≥40	1.68 (1.25-2.27)
Sex, male vs female	1.32 (0.99-1.75)
Disease duration, numerical, per year increment	0.96 (0.93-0.99)
24 months pre-baseline relapse activity, numerical, per additional relapse	2.50 (2.10-2.97)
EDSS score, categorical, ≥3 vs <3	3.13 (2.12-4.39)
MRI ≥10 vs <10 T2 lesions	2.10 (1.50-2.93)

Patients treated with rituximab or "other" DMTs are excluded from this analysis (n=42). EDSS: Expanded disability status scale; MRI: Baseline MRI T2-weighted lesions.

The crude odds ratio is shown as well as odds ratios adjusted for the covariates: age, sex, disease duration, EDSS score at treatment start, 24 months pre-baseline relapse activity and baseline MRI T2-weighted lesions (<10 vs ≥10). Both age and sex remained a significant factor with all adjustments and the odds ratio did not change considerably when also MRI was included as covariate.

3.2. Adherence to therapy

After a median follow-up time of 45 months for patients younger than 40 years and 46 months for patients 40 years or above, 1,658 out of 3,497 (47 %) patients were still adherent to the initial therapy (Table e-3). In those patients who were still adherent to the initial therapy, the median treatment time was 30 months in both the 791 (42 %) adherent patients below 40 years and the 867 (54 %) adherent patients aged 40 years or above (Table e-3). A lower proportion of the women were adherent to the initial therapy (45 %) compared to men (53 %) (Table e-3).

Comparing adherence to the initial treatment more patients were adherent to heDMTs than to meDMTs (Table 4). Patients 40 years or above were more prone to stay on the initial treatment compared to patients below 40 regardless of the initial treatment being meDMT ($p<0.001$) or heDMT ($p=0.008$) (Table 4).

Adherence to different DMTs is shown in Table e-4 for patients < 40 years and patient ≥ 40 years. The longest adherence was seen in patients treated with injectable platform therapies (interferon-beta preparations or glatiramer acetate), while the shortest adherence times were seen for the latest approved DMTs, cladribine and ocrelizumab. Apart from a trend towards longer adherence in patients ≥ 40 years in patients treated with teriflunomide, only small differences were seen between approved DMTs.

Table 4
Adherence to initial therapy in patients treated with moderate efficacy treatment* vs. high efficacy treatment**, stratified according to age <40 years (*N*=785) or ≥40 years (*N*= 855).

	<40 years old		≥40 years old		*p*-value***
	Numbers started	Numbers adherent (%)	Numbers started	Numbers adherent (%)	
Moderate efficacy treatment*	1,564	587 (38)	1,433	738 (52)	<0.0001
High efficacy treatment**	306	198 (65)	152	117 (77)	0.008

Patients treated with rituximab or "other" DMTs are excluded from this analysis (*n*=18).
* inj. platform therapies (interferon-beta 1a sc., interferon-beta 1a im., interferon-beta 1b, glatiramer acetate), teriflunomide, or dimethyl fumarate
** Natalizumab, fingolimod, alemtuzumab, cladribine, or ocrelizumab
*** For the association between adherence and age. Based on Chi-Square test.

3.3. Treatment escalation

In total, 693 out of 2,997 patients experienced a relapse while on treatment with the initial meDMT (Table 5). Relapse activity resulted in escalation of therapy to a heDMT in 432 (62 %) patients, with a significant difference between escalation of therapy compared to no escalation when comparing patients aged < 40 years (*N*=273, (67 %)) and patients aged 40 years or above (*N*=159 (56 %)) (*p*=0.008).

Table e-5 and Table e-6 show the effect of age (<40 vs ≥40) and sex (male vs female) on the probability of treatment escalation to a heDMT in patients with relapse activity on the initial meDMT (as compared to patients changing to another meDMT or continuing on the same DMT) (*N*=668). The crude odds ratio is shown as well as odds ratios adjusted for the covariates: age, sex, disease duration, EDSS score and number of relapses 24 months prior the initial moderate efficacy therapy. Male patients were more likely to have treatment escalation to heDMTs (fully adjusted odds ratio 2.03), while younger patients had higher odds of escalating therapy to a heDMT compared to older patients (fully adjusted odds ratio 1.49).

4. Discussion

Overall, the choice of initial therapy between a meDMT and a heDMT should be guided by the patient's known prognostic factors in relation to the benefit / risk ratio of the therapy, and the final choice should be made in partnership with the patient. The patient's prognostic factors comprise clinical disease activity, defined as number and severity of relapses in the one or two years prior to start of therapy; the number of hyperintense T2 lesions or of gadolinium enhancing lesions in brain MRI; and the number of spinal cord lesions at the time of treatment initiation (Maniscalco et al., 2020; Sacca et al., 2019). Other possible prognostic factors influencing the choice of initial treatment intensity may include age, EDSS disability or rate of disability worsening, which could be expressed as the Multiple Sclerosis Severity Scale score, and the presence of comorbidities as well as the individual patient's preference has to be taken into consideration (Kalincik et al., 2017; Magyari and Sorensen, 2020). As patient preferences always should be taken into consideration when choosing the DMT, it is of interest that patient preferences might differ from the neurologist's advice based on prognostic factors. A recent British study showed that the route of drug administration was the strongest determinant of preference (27%; relative importance out of 100%), followed by relapse free rate (21%) and symptom progression (14%). Once-daily oral treatment was preferred over all other methods of administration (Bottomley et al., 2017).

Traditionally, the meDMTs are considered safer than the heDMTs, although some of the new heDMT also appear to have an advantageous risk / benefit ratio (Soelberg Sorensen, 2017).

Age can be considered a factor responsible for change in relapse rate, recovery from relapses, faster worsening of permanent symptoms and immunosenescence that may influence therapeutic efficacy and choice of DMT (Kalincik et al., 2017; Matell et al., 2015; Signori et al., 2015). Sex has traditionally not been considered a major risk factor although men appear to have a more rapidly worsening disease course and, in some reports, less beneficial effect of DMTs (Bove and Chitnis, 2014; Bove et al., 2016).

In the 3,497 patients, who started their first DMT after January 1st, 2014, we found, as expected, that high clinical and MRI disease activity and high EDSS score were important determinants for the choice of therapy, but also that age was a major factor in choice of treatment intensity at almost similar odds ratio as that of relapses and MRI activity prior to treatment start. Patients < 40 years had 1.69 higher odds of being treated with a heDMT and men had higher odds of being treated with a heDMT compared to women (odds ratio 1.53). Contrary to the other heDMTs, ocrelizumab was prescribed at the same rate in patients below the age of 40 years and patients 40 years and above. Most likely it reflects differences in the prescribing neurologists' preferences. One contributory cause could be that ocrelizumab sometimes is used in patients with suspected transition to progressive MS and these patients are in general older than 40 years.

In the subgroup of 1,741 patients, in whom data on baseline MRI were available, the odds ratio between patient below and above 40 years of age was comparable to that of the total population (odds ratio 1.68), whereas the effect of clinical or MRI activity was slightly higher (odds ratio 2.10) and the odds ratio of 1.32 between men and women was lower with borderline significance. This subgroup of patients had shorter disease duration and were more often on heDMT. In the Danish population, we have observed a clear trend towards more frequent choice of a heDMT as the initial treatment in highly active patients and of escalation to a heDMT in case of breakthrough disease on a meDMT.

Previous studies have shown reduced therapeutic efficacy on disability worsening of some DMTs in older patients (Weideman et al., 2017). In patients treated with natalizumab, only patients below the age of 40 years showed a beneficial effect on EDSS worsening (Hutchinson et al., 2009) and patients below the age of 50 years had a significantly greater reduction in EDSS scores and MSSS and were less likely to stop therapy for lack of efficacy compared to older patients (Matell et al.,

Table 5
Choice of subsequent therapy in 693 patients who on treatment with the initial moderate efficacy DMT experienced a relapse stratified according to age <40 years (*N*=410) or ≥40 years (*N*=283).

Treatment choice	<40 years old	≥40 years old	All patients	*p*-value****
Treatment escalation*	273 (67)	159 (56)	432 (62)	0.008
Lateral change of DMT**	47 (11)	31 (11)	78 (11)	
Continued same DMT	77 (19)	81 (29)	158 (23)	
Stopped therapy***	13 (3)	12 (4)	25 (4)	
Total number of patients	410 (100)	283 (100)	693 (100)	

* change to a high efficacy therapy (including daclizumab, ofatumumab and rituximab).
** change to another moderate efficacy therapy.
*** stopped therapy temporarily (> 6 months) or permanently.
**** For the association between escalation vs no escalation (lateral change or continuation) and age. Based on Chi-Square test.

2015).

Subgroup analysis of the FREEDOMS trial showed that fingolimod 0.5 mg daily significantly reduced the annualized relapse rate in patients < 40 years but not in patients ≥ 40 (Devonshire et al., 2012).

In the CAMMS study, the effect of alemtuzumab on sustained reduction in disability was only seen in patients below the age of 31 (Coles et al., 2011), and in the OPERA I and II trials ocrelizumab was more effective in reduction of the annualized relapse rate in patients below the age of 40 years (Turner et al., 2019).

In a meta-analysis of 6 randomized, phase III trials of DMTs, patients < 40 years had more relapse reduction and less disability worsening than older patients (Signori et al., 2015).

Accordingly, a large multicenter study based on real-world data analyzed predictive factors for individual treatment response and found that higher age at treatment start predicted a higher relapse incidence and EDSS worsening (Kalincik et al., 2017).

Regarding sex differences, natalizumab was more effective on relapse activity in women than in men (Hutchinson et al., 2009) and teriflunomide only showed a significant effect on relapse rate in women and not in men (Miller et al., 2012).

However, a systematic review of fourteen studies, 11 randomized controlled trials and 3 cohort studies including 11,425 participants, concluded that although the studies did occasionally show sex-specific differences for some clinical outcomes in patients with MS who received DMTs, the limitation of subgroup analysis design made it difficult to draw conclusions on the direction or the extent of the sex-based effect. Hence, no clear sex-based differences in response to DMTs have been documented to date (Li et al., 2017).

Adherence to therapy was relatively high as 47% percent of the patients were still adherent to the initial therapy after a median follow-up period of 46 months. Adherence was higher in patients above 40 years in both the meDMT and heDMT group of patients, which in the meDMT group could be at least partly explained by the smaller proportion of patients older than of 40 years who compared with those younger than 40 years escalated therapy in case of clinical activity.

Adherence is influenced by several factors of which convenience, adverse effects and effectiveness of DMTs are among the most important. Another reason for adherence to the initial treatment in older patients could be the neurologist's perception of safety issues in older patients which may instigate the neurologist to stay with a meDMT perceived to be safer than heDMTs. Further, an additional reason could be the presence of comorbidities that increases in prevalence with increasing age (Magyari and Sorensen, 2020).

This is in accordance with the results of a Finnish study reporting that males and older patients were more likely to remain on the same treatment (Lahdenpera et al., 2020), and a Veteran Administration study also showed that adherence was less in patients younger than 59 years of age (Gromisch et al., 2020). In a study of patients sampled from the North American Research Committee on Multiple Sclerosis (NARCOMS) registry, younger patient had higher risk of non-adherence (Thach et al., 2020), and younger age was a predictor of switch of therapy because of inefficacy, while switch because of tolerance or safety issues was not influenced by age (Sacca et al., 2019)

Several other studies have corroborated that younger age increases the odds of treatment withdrawal (Ferraro et al., 2018; Melesse et al., 2017; Warrender-Sparkes et al., 2016; Zettl et al., 2017)

We found that escalation of therapy in patients who experienced a relapse on a meDMT was more frequently seen in men than in women and in younger patients than in older. Women may be more inclined to stay on a platform therapy because of pregnancy planning. However, in general treatment escalation should be established in any case of sub-optimal therapeutic response to a meDMT as treatment escalation to a heDMT leads to fewer relapses compared with remaining with the same meDMT or switching to another meDMT (Chalmer et al., 2019; Dorr and Paul, 2015; He et al., 2015; Spelman et al., 2015).

We have tested the dataset for interactions between the key variables and did not find any apart from a weak interaction between sex and age.

Studies have suggested that there are differences in the prescription pattern between neurologists. Sex did not influence the pattern, whereas older age, less years of experience, less MS patients seen per week and nationality seemed to delay treatment initiation and escalation of therapy in case of clear evidence of clinical and radiological disease activity (Almusalam et al., 2019; Saposnik et al., 2018). We were not able to control for differences in in the prescription pattern among the Danish neurologists, but variations might probably be reduced as DMTs can only be prescribed at specialised MS clinics in public hospitals and treatment is implemented according to common treatment guidelines.

The strength of our study is the nationwide cohort comprising all Danish patients treated with DMT and the prospectively collected real-time data.

A limitation of our study is the incomplete registration of MRI data, which were only available in approximately half of the patients starting on their first DMT and even less in patients who were monitored on treatment with a meDMT. Although patients on DMT have undergone a yearly MRI, the MRI data were only entered into the register during the most recent years. Another limitation is the lacking possibility of controlling for unknown and unmeasured confounders, e.g. the neurologists' and patients' personal preferences regarding choice of initial DMT. One of these possible confounders may be the reluctance of neurologists to choose an initial heDMT or to increase treatment intensity in older patients who may approach the secondary progressive phase of the disease. Furthermore, subgroup and post-hoc analysis should always be interpreted with caution given multiplicity problems and small sample sizes (Tanniou et al., 2016).

5. Conclusions

The choice of initial therapy and treatment escalation depends on many factors that interact in a complex pattern and include disease characteristics like duration, disease burden and activity, and other prognostic factors; the efficacy and safety of DMTs; patient characteristics and therapeutic preferences; the neurologist's personal treatment preferences; and the availability of DMTs according to local regulations and reimbursement. Some of these factors are known and others only partly known or unknown.

However, age and sex appear to be independent determinants for the choice of the initial DMT and for the decision of treatment escalation in patients with breakthrough disease on a meDMT. It is unfortunate if older age is a factor that make choice of a heDMT less likely, as many DMTs seems to be less efficacious in older patients, which could be a good reason to initiate treatment with a heDMT in these patients. As the age of the population of relapsing-remitting MS patients is increasing both because of a higher age at disease onset and a prolonged RRMS course (Koch-Henriksen et al., 2018), neurologists should pay attention to selecting the appropriate therapy based on positive and negative prognostic factors when a new treatment is initiated.

The long-term risks are a key issue when using heDMT as the first treatment in young patients, and the unknown long-term risks of the more recent DMTs, the oral meDMTs, alemtuzumab, cladribine and ocrelizumab need to be weighed against the long-term benefits of the drug. The long-term risks and benefits can only be assessed from real-world data, and high-quality register data would be crucial in this respect.

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CRediT authorship contribution statement

Per Soelberg Sorensen: Conceptualization, Methodology, Writing -

original draft. **Tine Iskov Kopp:** Formal analysis, Methodology, Writing - original draft. **Hanna Joensen:** Resources, Data curation, Writing - review & editing. **Anna Olsson:** Writing - review & editing. **Finn Sellebjerg:** Writing - review & editing. **Melinda Magyari:** Writing - review & editing.

Declaration of Competing Interest

P. S. Sørensen has received personal compensation for serving on scientific advisory boards, steering committees, independent data monitoring committees or have received speaker honoraria for Biogen, Merck, Novartis, TEVA and Celgene/BMS. **T. I. Kopp** has received honoraria for participating in advisory board from Novartis and received support to congress participation from Biogen. **Joensen** has received honoraria for participating in advisory board from Biogen. **A. Olsson** has received support for congress participation from Roche and Novartis. **F. Sellebjerg** has served on scientific advisory boards for, served as consultant for, received support for congress participation or received speaker honoraria from Alexion, Biogen, Merck, Novartis, Roche and Sanofi Genzyme. His laboratory has received research support from Biogen, Merck, Novartis, Roche and Sanofi Genzyme. **M. Magyari** has served on scientific advisory board for Biogen, Sanofi, Roche, Novartis, Merck, Abbvie, Alexion has received honoraria for lecturing from Biogen, Merck, Novartis, Sanofi, Genzyme, has received research support and support for congress participation from Biogen, Genzyme, Roche, Merck, Novartis.

Supplementary materials

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