Is there an impact of early initiation of disease-modifying therapies in patients with relapsing-remitting multiple sclerosis in the German registry?

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Introduction

- Relapsing–remitting multiple sclerosis (RRMS) is a chronic neurological disease that can lead to accumulating disability.[1,2]
- Several disease-modifying therapies (DMTs) are available for treatment with RRMS; previous studies suggest that early medical intervention with these therapies may help to delay disease progression.[3,4]
- This study aimed to provide further insight into the impact of early treatment with DMTs on relapse rate and disease severity in patients with RRMS.

Objective

- To study the baseline demographics and disease characteristics and the treatment outcomes, over a 5-year period, in patients with RRMS who received DMTs, comparing early and late treatment initiation.

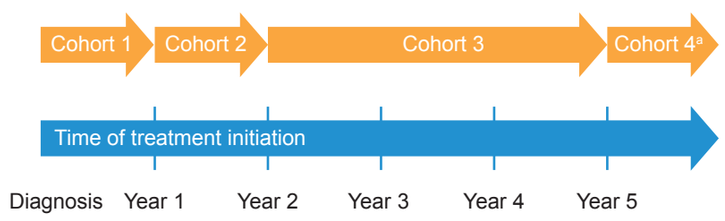
Methods

- Data were obtained from the multiple sclerosis disease registry of the German NeuroTransData network of neurologists and psychiatrists.
- Patients who initiated a DMT between 1 January 2009 and 1 October 2021 were included. Patient cohorts were defined based on the time of initiation of first DMT (index date) relative to the date of diagnosis (**Figure 1**).
- Outcome data were censored at discontinuation of or switching from the first DMT, or 5 years after the diagnosis date (whichever came first).
- Treatment outcomes were assessed using annualized relapse rate (ARR) and Expanded Disability Status Scale (EDSS) scores in a 5-year analysis window that began at the index date.

Results

- Patient cohorts were defined based on the time of initiation of their first DMT relative to the date of RRMS diagnosis: cohort 1, within 1 year (n = 5048); cohort 2, between 1 and 2 years (n = 559); cohort 3, between 2 and 4 years (n = 788); cohort 4, after 5 years (n = 1604) (**Figure 1**).

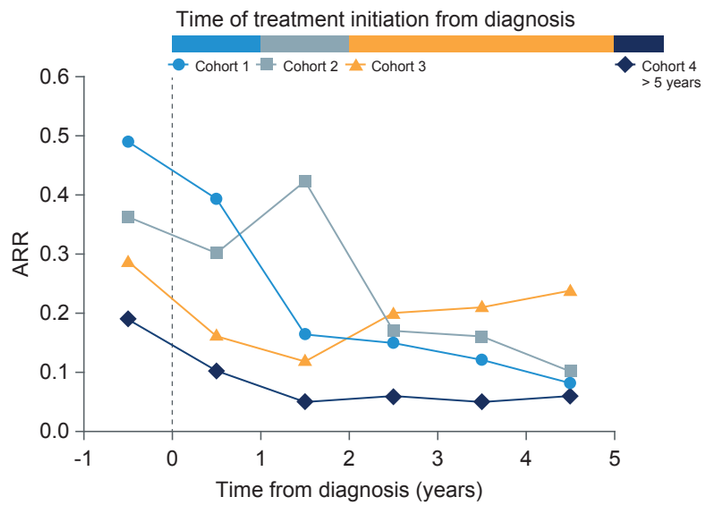
Figure 1. Cohort categorization



[a]Patients in cohort 4 did not initiate DMTs until after 5 years from diagnosis and therefore did not receive a DMT during the evaluation period used in this study.
DMT, disease-modifying therapy.

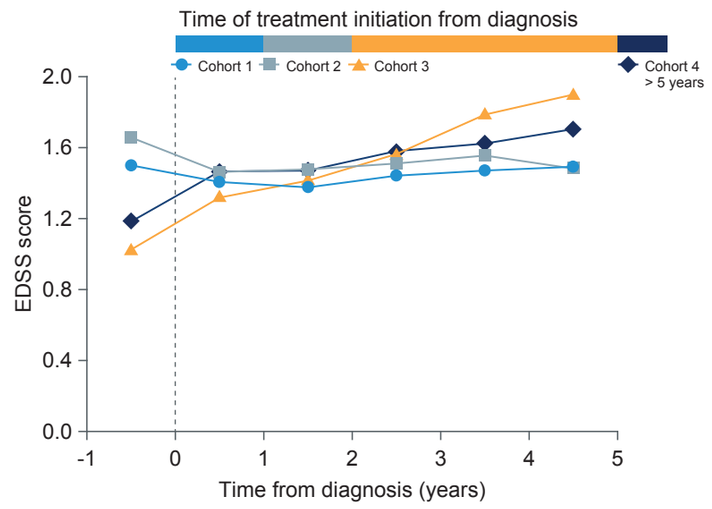
- No major differences were found among the cohorts in age, time since symptom onset or baseline EDSS score (**Table 1**).
- Relapses were associated with DMT initiation, with 43.6% of patients in cohort 1 experiencing at least one relapse in the 12 months before the index date compared with 31.3%, 27.2% and 18.1% of patients in cohorts 2, 3 and 4, respectively (**Table 1**).
- Of the four cohorts, cohort 1 received glatiramer acetate and interferons most commonly (74.4%) and cohort 4 received these DMTs least commonly (54.4%) (**Table 1**).
- The use of other DMTs, including monoclonal antibodies, broadly increased with increased time to DMT initiation (**Table 1**).
- For cohorts 1 and 2, baseline mean (standard deviation [SD]) ARR was 0.5 (0.6) and 0.4 (0.6) respectively, declining to 0.1 (0.3) and 0.1 (0.3) by the fifth year after diagnosis. In contrast, patients in cohort 3 and 4, who did not receive DMT until at least 2 years after diagnosis, had lower baseline mean ARRs of 0.3 (0.5) and 0.2 (0.4), respectively.
- At year 5 after diagnosis, the reductions in ARR from baseline for cohorts 3 and 4 were smaller than those for cohorts 1 and 2 (**Figure 2**).
- For patients in cohorts 3 and 4, EDSS scores increased from baseline over the 5-year study period. In contrast, EDSS scores for patients in cohorts 1 and 2 did not increase over the 5-year study period (**Figure 3**).
- However, these EDSS results must be interpreted with caution owing to a high level of missing data in our data set (**Table 2**).

Figure 2. ARRs by time from diagnosis for cohorts who initiated DMTs at different times following diagnosis



Each data point represents the mean score over the 12-month period.
ARR, annualized relapse rate; DMT, disease-modifying therapy.

Figure 3. EDSS scores by time from diagnosis for cohorts who initiated DMTs at different times following diagnosis



Each data point represents the mean score over the 12-month period.
DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale.

Table 1. Baseline demographics and disease characteristics of patients with RRMS

Demographic or characteristic	Cohort 1 n = 5048	Cohort 2 n = 559	Cohort 3 n = 788	Cohort 4 n = 1604
Age at index date, years, mean (SD)	35.3 (10.4)	35.9 (10.5)	35.5 (10.1)	32.4 (8.9)
Sex, female, n (%)	3556 (70.4)	414 (74.1)	554 (70.3)	1227 (76.5)
Time since symptom onset, years, mean (SD)	1.89 (4.1)	1.86 (3.9)	2.17 (4.67)	2.02 (4.12)
EDSS score ± 3 months of index date, mean (SD)	1.39 (1.21)	1.71 (1.47)	1.13 (1.2)	1.26 (1.42)
Patients with missing EDSS score, n (%)	3278 (64.9)	495 (88.6)	737 (93.5)	1558 (97.1)
ARR in the 12 months before index date, mean (SD)	0.5 (0.6)	0.4 (0.6)	0.3 (0.5)	0.2 (0.4)
Number of relapses in the past 12 months, n (%)				
0	2848 (56.4)	384 (68.7)	574 (72.8)	1313 (81.9)
1	1949 (38.6)	152 (27.2)	201 (25.5)	283 (17.6)
2	229 (4.5)	20 (3.6)	13 (1.6)	7 (0.4)
3	19 (0.4)	3 (0.5)	0 (0)	1 (0.1)
> 3	3 (0.1)	0 (0)	0 (0)	0 (0)
First DMT, n (%)				
Interferon	2513 (49.8)	243 (43.5)	320 (40.6)	564 (35.2)
Glatiramer acetate	1242 (24.6)	127 (22.7)	176 (22.3)	309 (19.3)
Dimethyl fumarate	622 (12.3)	82 (14.7)	105 (13.3)	248 (15.5)
Teriflunomide	322 (6.4)	40 (7.2)	65 (8.2)	170 (10.6)
Fingolimod	118 (2.3)	26 (4.7)	49 (6.2)	128 (8.0)
Natalizumab	97 (1.9)	20 (3.6)	42 (5.3)	73 (4.6)
Ocrelizumab	50 (1.0)	11 (2.0)	8 (1.0)	27 (1.7)
Other[a]	84 (1.7)	10 (1.8)	23 (2.9)	85 (5.3)

[a]Includes alemtuzumab, azathioprine, cladribine, cyclophosphamide, daclizumab, immunoglobulins, laquinimod, methotrexate, mitoxantrone, ofatumumab, ozanimod, rituximab and siponimod.
ARR, annualized relapse rate; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; RRMS, relapsing–remitting multiple sclerosis; SD, standard deviation.

Table 2. Availability of EDSS scores per year relative to treatment initiation

Time span	Proportion of patients with EDSS score per year relative to index date, %			
	Cohort 1 n = 5048	Cohort 2 n = 559	Cohort 3 n = 788	Cohort 4 n = 1604
−1 year to index date	16.8	8.6	6.4	2.7
Index date to 1 year	63.3	25.6	12.6	3.6
1 year to 2 years	68.0	58.8	16.6	3.2
2 years to 3 years	72.3	62.8	32.8	3.7
3 years to 4 years	73.2	65.8	48.4	5.1
4 years to 5 years	75.5	64.4	64.7	6.3

EDSS, Expanded Disability Status Scale.

Key messages

- Across cohorts, higher initial ARRs were generally associated with a greater ARR reduction.
- Patients with delayed treatment start (cohorts 3 and 4) had low ARRs in the fifth year after diagnosis.
- EDSS progression in the 5 years after diagnosis seems to be largely independent of time of treatment initiation.
- Cohort 3, who initiated DMT 2–5 years after diagnosis, had the least favourable ARR and EDSS over time.

Conclusions

- **Neurologists appear to make a reasonable prognosis regarding the dynamics of the disease over a 5-year period and whether to initiate treatment or wait and see clinical changes.**
- **Timing of DMT initiation seems to be largely triggered by relapse activity in all cohorts.**
- **A potential trade-off with the wait and see approach is the more widespread use of DMTs other than glatiramer acetate and interferons for patients who initiated treatment later.**
- **Disability remained fairly stable among those who initiated DMT treatment within the first 2 years of diagnosis but seem to worsen more for those initiating DMTs later.**
- **The benefit-risk ratio of treatments may be an important consideration along with other disease-related factors in individualizing patient treatment decisions.**

Disclosures

SB has received fees from Kassenärztliche Vereinigung Bayern and health maintenance organizations for patient care; fees for consulting, project management, clinical studies and lectures from Biogen, Lilly, Merck, NeuroTransData, Novartis, Roche and Thieme Verlag; and compensation as a board member of NeuroTransData. AD is contracted to perform statistical projects from NeuroTransData. AB has received fees for consulting, advisory board membership, speaking and other activities from NeuroTransData; fees for project management, clinical studies and travel from Novartis and Servier. MS is an employee of Janssen-Cilag GmbH, a pharmaceutical company of Johnson & Johnson, and may hold stock or stock options in Johnson & Johnson. MA-T, HHL, AK and KG are employees of Janssen Pharmaceuticals, a pharmaceutical company of Johnson & Johnson, and may hold stock or stock options in Johnson & Johnson. JvD is an employee of Janssen-Cilag B.V., a pharmaceutical company of Johnson & Johnson, and may hold stock or stock options in Johnson & Johnson.

Acknowledgements

The study was funded by Janssen Pharmaceuticals, a pharmaceutical company of Johnson & Johnson. Medical writing support was provided by Valentina Bart PhD of PharmaGenesis Cardiff, Cardiff, UK in accordance with Good Publication Practice 3 (GPP3) guidelines (http://www.ismpp.org/gpp3). Yanic Heer of Rewoso AG, Zurich, Switzerland was contracted to perform data analysis and contributed to the preparation of the poster.

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Presented at the 38th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), 26–28 October 2022, Amsterdam, Netherlands