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The impact of drug diversity on treatment effectiveness in relapsing-remitting multiple sclerosis (RRMS) in Germany between 2010 and 2018: real-world data from the German NeuroTransData Multiple sclerosis registry

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Abstract

Objective

To evaluate the impact of drug diversity on treatment effectiveness in relapsing-remitting multiple sclerosis (RRMS) in Germany

Design

This study employs real world data captured in-time during clinical visits in 67 German neurology outpatient offices of the NeuroTransData (NTD) MS registry between 1 Jan 2010 and 30 Jun 2019, including 237,976 visits of 17,553 RRMS patients. Adherence and clinical effectiveness parameters were analyzed by descriptive statistics, time-to-event analysis overall and by disease modifying therapies (DMTs) stratified by administration modes (injectable, oral and infusion). Three time periods were compared: 2010–2012, 2013–2015, and 2016–2018.

Results

Between 2010 and 2018, an increasing proportion of RRMS patients were treated with DMTs and treatment was initiated sooner after diagnosis of MS. Introduction of oral DMT temporarily induced higher readiness to switch. Comparing the three index periods, there was a continuous decrease of annualized relapse rates, less frequent EDSS progression and increasing periods without relapse, EDSS worsening and with stability of no-evidence-of-disease-activity (NEDA) 2 and 3 criteria, lower conversion rates to secondary progressive MS (SPMS) on oral and on injectable DMTs.

Conclusion

Sparked by the availability of new mainly oral DMTs, RRMS treatment effectiveness improved clinically meaningful between 2010 and 2018. As similar effects were seen for injectable and oral DMTs more than for infusions, a better personalized treatment allocation in many patients is likely. These results indicate that there is an overall beneficial effect for the whole MS patient population as a result of the greater selection of available DMTs, a benefit beyond the head-to-head comparative efficacy, resulting from an increased probability and readiness to individualize MS therapy.

Introduction

The field of multiple sclerosis (MS) treatment have seen dynamic developments over the last three decades. 1. Since the introduction of the first interferon-β1a (IF-b1a) in 1994, treatment options for patients with relapsing remitting MS (RRMS) have expanded to 14 different disease modifying therapies (DMTs) registered in Europe. 2. Regulatory authorities have defined new MS subgroups such as high-disease activity course of RRMS, relapsing MS (RMS), RRMS and relapsing forms of secondary progressive MS, for the definition of drug labels 3. Regulatory authorities have also developed legislative and administrative initiatives such as the "AMNOG procedure" to control costs of drugs, in the face of drug costs in Germany raising from €30.2 billion to €43.9 billion from 2010–2018.[1] 4. Patients, physicians and payers expect allocation of the most effective DMT for the individual patient while minimizing adverse events. While reduction of relapse activity was the treatment goal in the 1990s, current treatment goals strive for "no evidence of disease activity".

However, little is known about the impact of these developments on real-world treatment pattern and effectiveness on disease activity in RRMS. This analysis investigates treatment pattern and effectiveness over time by comparing three time periods between 2010 and 2018 (defined by availability of new DMTs entering the German market) of real-world data from the physician´s network NeuroTransData (NTD) in Germany.

Methods

Database: the NTD multiple sclerosis registry

This project employed real-world clinical data captured by the NeuroTransData (NTD) multiple sclerosis registry. NTD is a Germany-wide physicians´ network founded in 2008 and run by physicians in the fields of neurology and psychiatry (www.neurotransdata.com). Governance principles are defined. NTD generates revenue by its members' participation in phase II–IV clinical trials, investigator initiated trials, and real-world data analytic projects in cooperation with pharmaceutical industry, payers and other players in the German and international health systems.

Currently, 132 specialists work in 67 NTD practices throughout Germany, serving approximately 600,000 outpatients per year. Each practice is certified according to network-specific and ISO 9001 criteria. An external certified organization audits compliance annually. The NTD MS registry includes approximately 25,000 patients with MS, representing about 15% of all MS patients in Germany. NTD captures demographic, clinical history, patient-related outcomes, and clinical variables in real time during clinical visits. Standardized clinical assessments of functional system scores and EDSS calculation are performed by certified raters (http://www.neurostatus.net). Data are entered into the web-based registry either manually or directly from digital sources.

Data quality is monitored by the NTD data management team, checking for inconsistencies and errors using an error analysis program. Both automatic and manually executed queries are implemented to further ensure data quality, e.g. checks for inconsistencies and requests for missing information. High data completeness is achieved by definition of minimum data sets, mandatory data entry fields, positive missing data confirmation. Advanced dynamic web-based data capturing, regular training of doctors and nurses, interactive chat forum for nurses and doctors, automated and manual feedback query system, daily-automated analysis of data plausibility and correctness, and annual on-site audit of procedures and source data by an external process quality certifier organization contribute to high data consistency. The NTD data capturing platform is also used as patient management system in the daily care of patients in NTD offices, thus guaranteeing timeliness of data.

All data are pseudonymized and pooled. The Institute for Medical Information Processing, Biometry and Epidemiology (Institut für medizinische Informationsverarbeitung, Biometrie und Epidemiologie (IBE)) at the Ludwig Maximilian University in Munich, Germany, manages codes and acts as an external trust center. Pooled data are stored on NTD servers and other NTD-controlled storage technology. This data acquisition and management protocol was approved by the ethical committee of the Bavarian Medical Board (Bayerische Landesärztekammer, June 14, 2012) and re-approved by the ethical committee of the Medical Board North-Rhine (Ärztekammer Nordrhein, April 25, 2017). Compliance with European and German legislation (BDSG, EU-DSGVO) is warranted including patient rights and informed consent requirements. Patient participation, informed consent procedures, data capturing, management and analytics fulfill the "Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology"[2], the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[3], the European Medicines Agency requirements for the "Use of patient disease registries for regulatory purposes – methodological and operational considerations"[4] and the ethical principles laid down in the Declaration of Helsinki[5].

Data for this project were captured between 1 January 2010 and 30 June 2019.

Data quality of the NeuroTransData Multiple Sclerosis registry

The main components for data quality of medical real-world data registries proposed by European Medicine Agency[4] are fulfilled by the NTD MS registry. The NTD also realizes the quality criteria of the EunetHTA REQueST (Registry Evaluation and Quality Standards Tool)[6] with 14 of 14 points in section "Methodological Information", 23 of 24 points in section "Essential Standards" and 5 of 6 points in section "Additional Requirements".

Data analysis

Analysis was performed in 3 time periods, reflecting different spectra of DMTs available during the respective period.

2010–2012 (index period 10–12): era of early treatment initiation at the stage of clinically isolated syndrome (CIS) with interferons and glatirameracetat and escalation with natalizumab approved since 2006 and fingolimod approved since 2011 for high-disease-activity (HDA) patients.

2013–2015 (index period 13–15): era of therapy diversification with introduction of alemtuzumab as an infusion for HDA patients, teriflunomide and dimetyhlfumarat as oral drugs for all stages of RRMS.

2016–2018 (index period 16–18): era of consolidated DMT spectrum. Cladribine, an oral HDA activity drug, was newly approved in August 2017. Daclizumab, which became available in July 2016, was restricted in July 2017 and withdrawn in March 2018, was not considered as numbers of patients were very small and a temporary distortion of results in the injectable group had to be excluded.

Parameters characterizing treatment acceptance and adherence were analysed for each index period.

Impact on treatment effectiveness was analyzed between 2010 and 2018 and for each index period for the strata “all DMT”, “injectables” including interferons-ß-1a, interferons-ß-1b, glatirameracetate, “orals” including fingolimod, teriflunomide, dimethylfumarate, cladribine, “infusions” including natalizumab, alemtuzumab, based on the European labels of these DMTs.

Treatment effectiveness was analysed for RRMS patients on DMT by annualized relapse rate (ARR), time-to-first-relapse on DMT, percentage of patients with 6 months confirmed disability-progression (6mCDP, CDP defined as at least 1.0-point EDSS score increases for patients with baseline EDSS score 0–5.5 EDSS and at least 0.5-point EDSS score increases for patients with baseline EDSS score greater than 5.5), time-to-6mCDP on DMT, time-from-first symptom to EDSS >=3-5 and >5 (in month), time-to-no-evidence-of-disease-activity (NEDA) 2 and 3 failure on DMT being started in the index periods. Risk rates for discontinuation were calculated as ratio of number of patients with discontinuation of DMT divided by all patients.

Patient and Public Involvement

There was no patient involvement.

Role of funding source

This study was conducted by NTD without additional funding or guidance by external sponsors.

Results

Data Quality

Exemplary frequencies of data captured constantly over time for several data items (see Table 1) underline the high data quality and consistency over time. The mean duration of follow-up was 5.07 years (SD 4.46). A total of 59,928 DMT treatment cycles were documented between 2010 and 2018.

Table 1. Numbers of patients with RRMS, visits per year and therapy cycles with DMTs captured in the NTD MS registry between 2010 and 2018. DMT, disease-modifying treatment; MRI, magnetic resonance imaging; RRMS, relapsing remitting multiple sclerosis.

Index year	Number RRMS patients	Visits documented per year	DMT cycles per year	Relapses per year	MRI per year
2010	5,170	16,377	4,168	1,821	3,096
2011	6,648	24,296	5,441	2,638	4,004
2012	7,017	23,298	5,893	2,600	3,107
2013	7,532	25,840	6,410	2,433	3,866
2014	7,591	28,261	7,536	2,076	3,989
2015	8,074	28,313	7,443	1,972	3,879
2016	8,401	29,715	7,566	1,795	3,781
2017	9,021	31,199	7,862	1,707	3,575
2018	8,946	30,677	7,609	1,487	4,102
2010–2018	68,400	237,976	59,928	18,529	33,399
Mean/patient/year		3.48	0.88	0.27	0.49

Patient Population

A total of 17,553 patients with RRMS were included (73.6% female, 26.4% male). Mean age at diagnosis of RRMS was 34 years (SD 10.66), mean annualized relapse rate between 2010 and 2018 was 0.27 (SD 0.6). Table 2 shows consistency and completeness of data in the three time periods between 2010 and 2018.

Table 2. Means and percentages of RRMS patient characteristics of the NTD MS registry in time periods between 2010 and 2018 at initiation of DMT (=index event). DMT, disease-modifying therapy MRI, magnetic resonance imaging; RRMS, relapsing remitting multiple sclerosis; SD, standard deviation.

Characteristic	10–12 (N=3,942)	13–15 (N=5,101)	16–18 (N=3,138)	All patients (N=12,181)
Female, %	73.17	73.74	26.26	73.07
Age, years (SD)	44.95 (10.21)	43.93 (10.88)	40.7 (11.03)	43.59 (10.94)
EDSS (SD)	2.12 (1.59)	2.10 (1.62)	1.89 (1.53)	2.05 (1.59)
Relapses before index event (SD)	1.93 (2.55)	2.26 (2.63)	2.21 (2.67)	2.14 (2.62)
Months MS duration (SD)	87.78 (85.87)	101.78 (93.62)	98.73 (94.99)	96.46 (91.75)
DMTs before index event (SD)	0.8 (1.01)	1.08 (1.14)	1.2 (1.26)	1.02 (1.14)
MRI around index event, %	39.93	43.5	37.38	40.77
MRI with progression around index event, %	20.83	20.78	18.36	20.17

Treatment acceptance

Overall proportions of RRMS patients actively treated with DMT increased steadily: 10–12, 70,7%; 13–15, 78.1%; 16–18, 80,1%. Proportions of DMT types by application changed during the 3 time periods 10–12/13–15/16–18 with percentages of patients on injectables 88/69/46, orals 13/44/54, infusions 12/10/10. Proportions of RMS patients receiving so-called high-disease activity DMTs increased continuously: 10–12, 23%; 13–-15, 27%; 16–18, 31%.

Initiation of DMT after diagnosis of RRMS

More patients started on a DMT within 6 months after diagnosis of RRMS (10–12, 62%; 13–15, 72%; 16–17, 66%), with shorter periods between first symptom and initiation of first DMT (10–12, 178 ±295 days; 13–15, 121 ±174 days; 16–18, 115 ±112 days). Orals were increasingly preferred as first DMT as they became available during the 3 periods

of time 10–12/13–15/16–18 with percentages of patients on injectables 74/44/40, orals 19/52/55, infusions 7/4/5.

Persistence on DMT

Availability of oral DMT increased the proportion of switches between DMTs from 16% of patients on treatment in 10–12 to 24% in 13–15, while in 16–18, 14% of patients on DMT switched. In parallel, time to discontinuation remained stable within these 3-years periods: in 10–12 mean time to discontinuation 8.49 months (SD 7.14); in 13–15, 8.10 months (SD 6.92); and in 16–18, 8.49 months (SD 7.71). There was a trend for patients staying longer on overall treatment for the most recent time period . This trend was driven by longer persistence of patients on infusion therapies in the most recent time period (Figure 1).

Figure 1. Time to discontinuation of DMTs in RRMS patients for time periods 2010–2012, 2013–2015, 2016–2018, all DMT (A) and by injectables (B), orals (C), infusions (D). DMT, disease-modifying treatments; RRMS, relapsing remitting multiple sclerosis

A. all DMT

B Injectables

C Orals

D Infusions

Non-medical reasons for discontinuation, such as patients´ perceptions and wishes, decreased over time from 71 to 51%. Lack of effectiveness is increased as a motivation for switching DMTs, as well as adverse events or pregnancy/family planning (Table 3).

Table 3. Reasons overall and risk rates by application type of DMT for discontinuation for three time periods 2010–2012, 2013–2015, and 2016–2018.
Non-medical reasons summarize patients´ perceptions and wishes. DMT, disease-modifying treatment; NA, not applicable as criteria was not captured.

Reasons for discontinuation, %	**10–12**	**13–15**	**16–18**
Antibodies/JCV-virus titer	1.28	1.85	1.51
amily planning	4.10	5.48	6.34
Adverse events	5.13	15.89	13.12
Lack of effectiveness	18.21	19.31	27.90
Freedom of disease activity	NA	0.34	0.36
Non-medical reasons	71.28	57.11	50.76
Risk rates for discontinuation			
Injectables	0.59	0.54	0.33
Orals	0.39	0.36	0.21
Infusions	0.59	0.37	0.17

Risk rates for discontinuation decreased continuously for all types of DMT over the three time periods, reaching a decrease of 44% for injectables, 46% for orals and 71% for infusions between 2010–2012 and 2016–2018.

DMT switching pattern

Patients increasingly switched from injectables to oral infusion DMTs, while switches to injectables decreased. Follow-on DMTs after oral DMTs were predominantly oral DMT. If infusion therapy was discontinued, almost all patients continued with oral DMTs (see Figure 2).

Figure 2. Percentage of switches between injectable, oral and infusion DMTs in RRMS for time periods A) 2010–2012, B) 2013–2015, C) 2016–2018. DMT, disease-modifying therapy; RRMS, relapsing remitting multiple sclerosis.

A

B

C

Treatment effectiveness

Relapse activity

Annualized relapse rate (ARR) decreased by a mean 39% overall, 40% for injectables and 30% for orals. Infusion therapies did not decrease (Figure 3).

Figure 3: Annualized relapse rate in three time periods 2010–2012, 2013–2015, 2016–2018 on DMT overall and by application type. DMT, disease-modifying therapy.

Proportions of patients documented with 6mCDP, with progression of EDSS <3 to ≥3–5 as well as from EDSS <5 to ≥5 decreased by 39% and 23%, respectively, between the first and the last time period analyzed. In parallel, times from first symptom of RRMS to reach the defined EDSS ranges increased by 22% and 15% respectively (see Table 4).

Table 4. Six months confirmed disability progression (6m CDP. EDSS increase of ≥1.0 for patients from previous EDSS): proportion of patients reaching EDSS >=3 to 5, reaching EDSS >=5 and months from first symptom of RRMS to 6mCDP in these strata.

	EDSS <3 to ≥3–<5	**EDSS <5 to ≥5**	**Months to 6mCDP EDSS ≥3-5**		**Months to 6mCDP EDSS ≥5**	
	% patients	% patients	Mean	SD	Mean	SD
10–12	1.02	0.26	122.30	81.03	181.59	92.17
13–15	0.76	0.31	130.95	85.60	181.37	110.04
16–18	0.62	0.20	149.26	93.32	209.73	97.70
Difference from 10–12 to 16–18, %	-39	-23	+22		+15	

Maintenance of NEDA 2 and 3 criteria

There was a clear trend that patients who initated DMTs for a minimum of 3 months in these index periods remained more frequently and longer free of disease activity according to NEDA 2 (no relapse, no 6mCDP) and NEDA 3 (no relapse, no 6MCDP, no MRI progression) criteria over the three periods of time (Figure 4).

Figure 4. A. Time to failure of no-evidence-of disease-activity (NEDA) 2 (no relapse, no confirmed disability progression) and B. NEDA 3 (no relapse, no 6months confirmed disability progression, no MRI worsening) criteria in RRMS patients on DMTs after a minimum treatment period of 3 months with treatment initiation within three time periods 2010–2012, 2013–2015, 2016–2018. DMT, disease-modifying treatment; MRI, magnetic resonance imaging; RRMS, relapsing remitting multiple sclerosis.

A.

B.

Mean times to NEDA 2 and 3 failure, censored for the 3 time periods, increased continuously. NEDA 2: 10–12, 6.92 months (SD 6.66); 13 –15, 7.10 months (SD 6.55); 16–18, 7.43 months (SD 7.11). NEDA 3: 10–12, 6.70 months (SD 6.41); 13–15, 7.16 months (SD 6,42); 16–18, 7.49 months (SD 6.89).

Progression to SPMS

Between 2010 and 2018, overall 2.34% of 176,553 patients switched from RRMS to SPMS during a mean follow-up time of 5.31 years. The mean time from first symptom of MS to SPMS was 214 months (SD 113.77), almost 18 years. Time-to-progression analysis did not reveal time differences between the 3 index time periods (not shown here). There was a continuous trend towards lower numbers of patients switching to SPMS while on DMT for at least 12 months from 4.25% in 10–12, to 1.97% in 13–15, and to 1.46% in 16–18.

Discussion

Medical guidelines, regulatory processes and public discussion in Germany and other countries regarding clinical benefits, treatment strategies and drug pricing are often focused on results from the randomized controlled trial (RCT) with an active comparator and versus placebo that led to registration of the drug[7]. However, clinical usage in a broad natural spectrum of patients and the increasing complexity of treatment options are causing a knowledge gap that RCTs are unable to fill. [Thus, qualified real-world-data (RWD) are increasingly employed to evaluate optimization of therapeutic strategies[8-11]. Translating DMT efficacy studies into evidence-based clinical practice by meta-analysis of 123 unique RRMS studies was extremely limited. One main limitations was the paucity of efficacy data beyond 3 years of treatment[12]. Other initiatives addressed methodological aspects of this efficacy–effectiveness gap between results of RCTs in selected patient groups and effectiveness in real-world usage[13]. This is the first study to address population effects of a series of newly introduced DMTs in RRMS on adherence and clinical effectiveness.

Transparent data quality is the key stone of any scientific project. The physician-owned NTD MS registry can demonstrate constant data density, including a mean of 3.5 patient visits documented over the last 9 years, based on a defined minimal dataset and high data quality. This was achieved by utilization of web-based in-time data capturing and continuous development of automated and manual quality assurance measures for capturing data from 8,000 to 9,000 RRMS outpatients per year in Germany.

Definition criteria of the three time periods chosen for this study are thought to reflect periods characterized by different sets of DMTs being available for the treatment of RRMS patients. Between 2010 and 2018 the broader spectrum, in particular of oral DMTs motivated more patients to initiate DMT treatment and start earlier after diagnosis of RRMS. Availability of oral DMTs temporarily increased switches between DMTs in the years after their introduction from 16% in 2010–2012 to 24% of patients on DMT in 2013–2015, with a decline back to 14% of patients switching between 2016 and 2018. This is also reflected in the time-to-discontinuation analysis, showing more frequent and quicker discontinuation of injectables in 2013–2015. Lack of effectiveness and adverse events may have gained in importance over time as reasons for discontinuation of DMT, mirroring increasing expectations of doctors and patients regarding benefit/risk of DMTs. Persistence on classes of DMTs after 3 years improved most noticeable for infusions in 2010–2012 moving from 50% to almost 80% in 2015–2018, injectables increasing from less than 10% to 60% and orals achieving stable persistence of about 72%. Risk rates for discontinuation decreased overall and for each application type.

Earlier initiation of treatment and more readiness to search for individual optimal therapy by switching between a greater diversity of drugs may have impacted treatment effectiveness. ARR decreased overall and for patients on injectables and orals aprroximately 30–40% between 2010–2012 and 2016–2018. However, there was no

change in ARR over time for infusions. Furthermore, worsening of disability could be controlled better in parallel. The proportion of patients with EDSS reaching total sum scores >3 and > 5 decreased by 39% and 23%, respectively, and times from diagnosis to the 6mCDPs increased by 22 and 15%, respectively, when comparing time periods 2010–2012 and 2016–2018.

Comparing treatment cycles initiated in these 3 time periods, these positive developments are also reflected by continuously increasing proportions of patients maintaining NEDA 2 and NEDA 3 criteria. In addition, proportions of patients on DMT switching from RRMS to SPMS decreased each time period, but mean times to SPMS from diagnosis of RRMS remained unchanged.

The parallel improvements of reduction in ARR and disability progression, longer maintenance of NEDA 2 and 3 status in all types of DMTs, independent of their application modes, indicate that the broader selection of DMTs enable a better individual disease control in RRMS. It can be reasonably assumed that the regulatory introduced definition of high-disease-activity-labels further supported a more stringent application of the therapeutic options available. As expected, better treatment is associated with longer persistence. The observation that more efficient therapies achieved lower relapse activity in parallel with slower disability progression and longer persistence on DMTs is in line with a previous MSBase registry-based report in smaller groups of RRMS patients with advanced EDSS scores between 3 and 6[14], as well as more recent data in earlier disease stages[15]. Beside the individual patient´s fate, this is of great socioeconomic relevance, as costs and utility in MS are highly correlated with disease severity[16] and progression inducing disease activity[17]. In contrast, continuing interferon-ß and glatirameracetate therapy 10 years or longer without optimization of therapy in response to disease activity results in an inevitable, almost linear increase in mean EDSS[18].

This study demonstrates a clinically meaningful, population-based benefit resulting from the availability of a broader selection of DMTs over time. The introduction of oral DMTs sparked a dynamic development between 2013 and 2015 with temporarily higher proportions of DMT switches but also more readiness to initiate DMTs earlier after diagnosis of MS. The similar extent of improvement of effectiveness parameter for oral and injectable DMTs demonstrates that this population effect is based on a more effective personalized allocation in individual patients.

Overall, these results indicate that there is an overall beneficial effect for the whole MS patient population as a result of the greater selection of available DMTs, a benefit beyond the head-to-head comparative efficacy, resulting from an increased probability and readiness to individualize MS therapy. Nevertheless, the challenge in daily practice is the quick identification of the individually most effective DMT at a given time during the course of MS, particularly in patients with persistent disease activity on their current DMT, especially regarding the immanent risk of developing SPMS. Promising techniques emerge based on biomarker like neurofilament light chain[19] or B-cell activity

response[20] or real-world-data-based statistical predictive algorithms[21]. As treatment decisions are driven currently by European label definitions, national cost control regulations and perceptions of physicians and patients, personalized-data-based decision support is required to further improve individual care.

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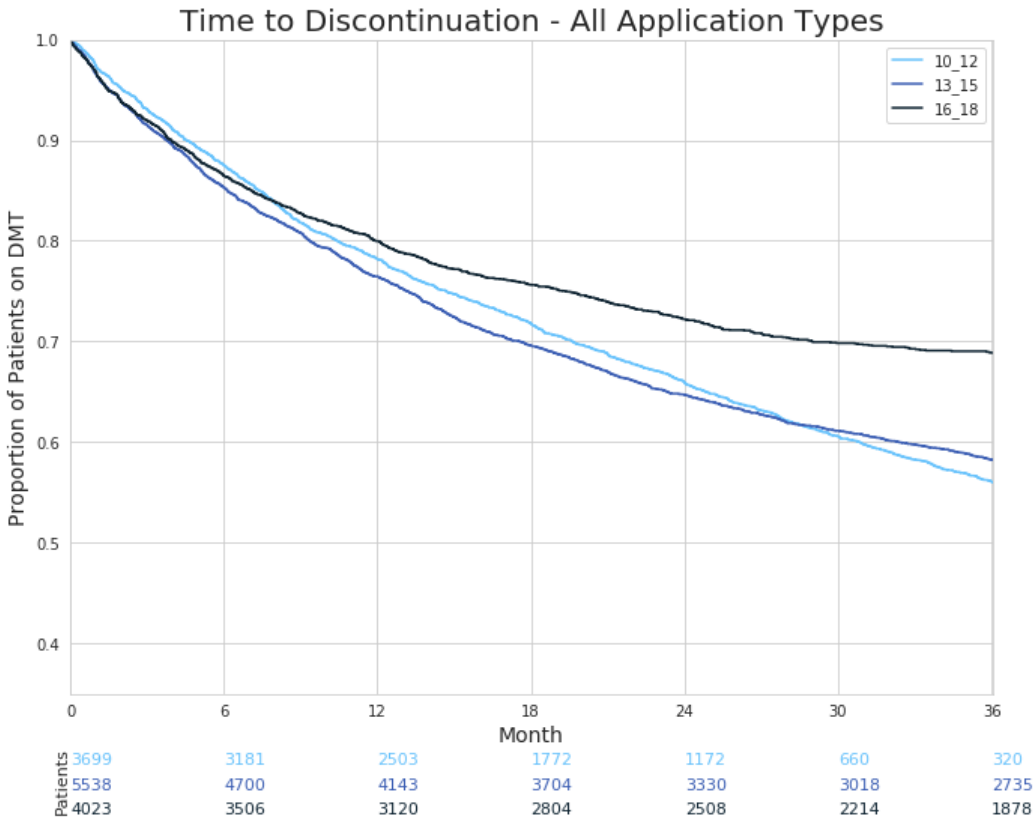
A.


Time to Discontinuation - All Application Types
Proportion of Patients on DMT
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0
6
12
18
24
30
36
Month
10_12
13_15
16_18
Patients
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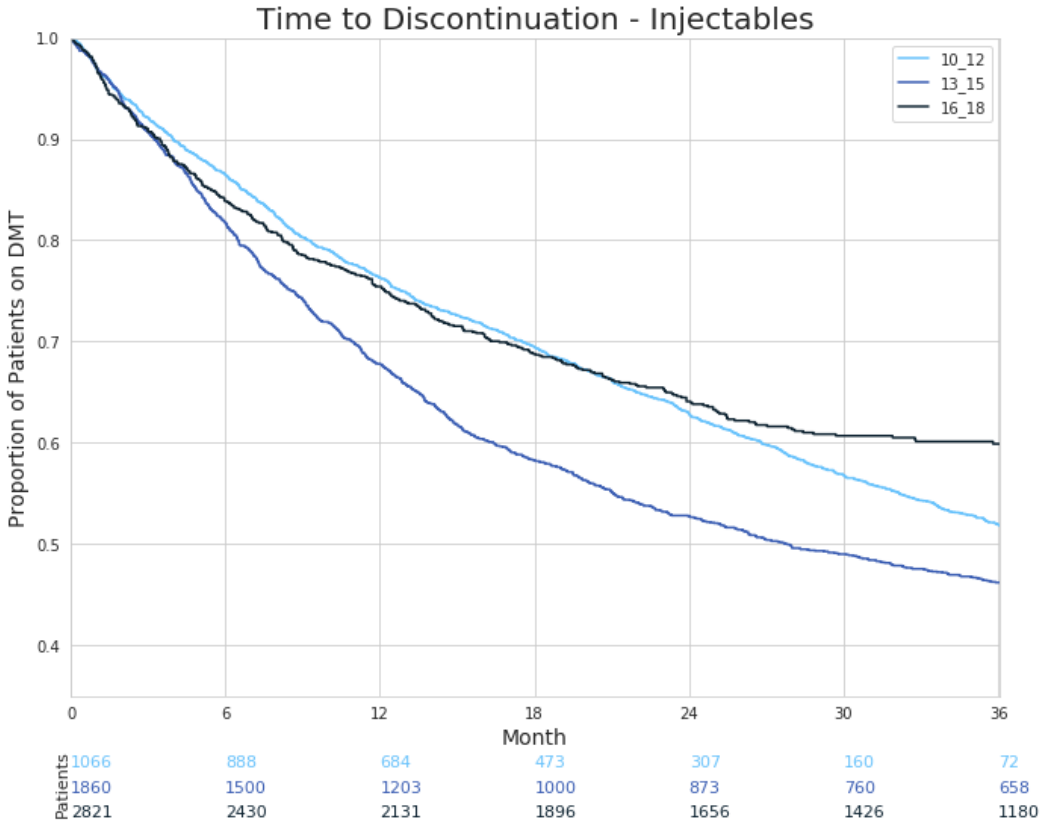
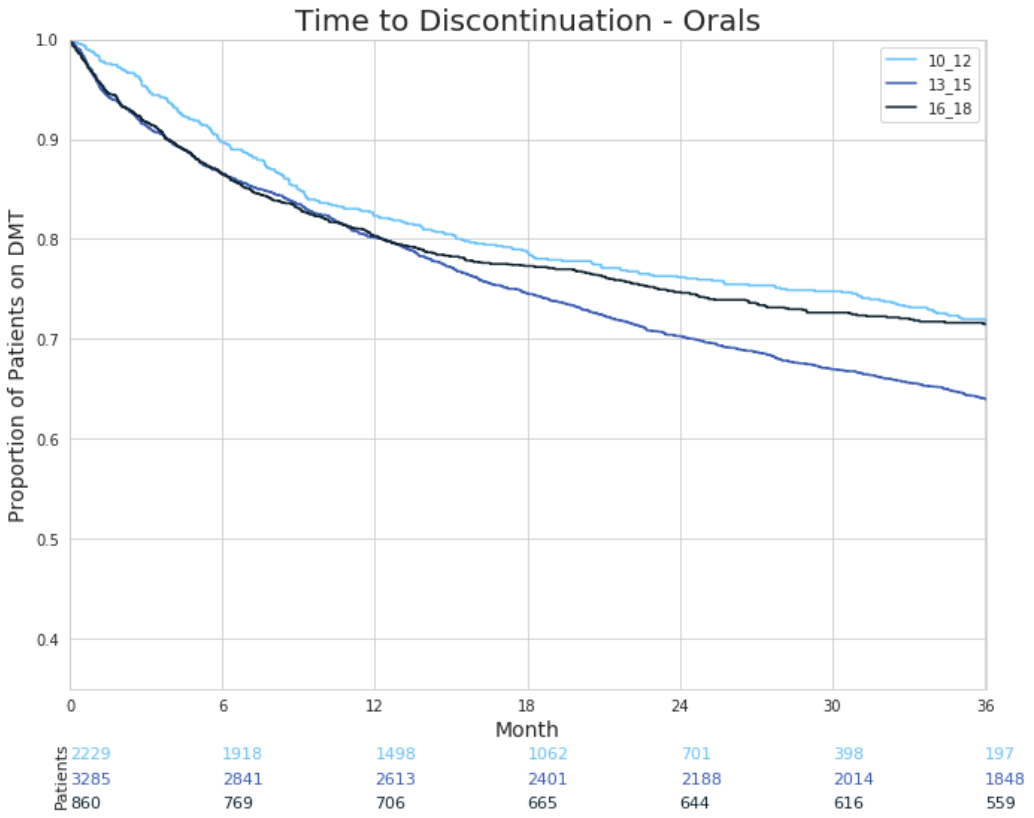
5538 4700 4143 3704 3330 3018 2735
4023 3506 3120 2804 2508 2214 1878

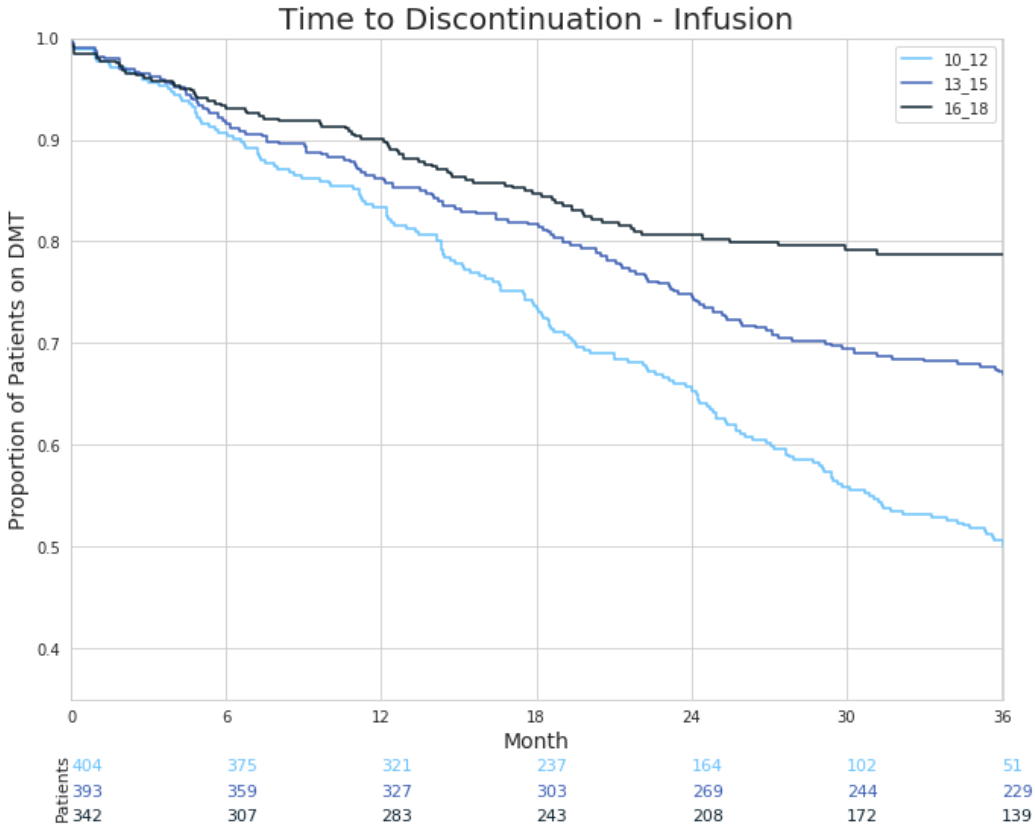
B.


Time to Discontinuation - Injectables
Proportion of Patients on DMT
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0
6
12
18
24
30
36
Month
10_12
13_15
16_18
Patients
1066 888 684 473 307 160 72
1860 1500 1203 1000 873 760 658
2821 2430 2131 1896 1656 1426 1180

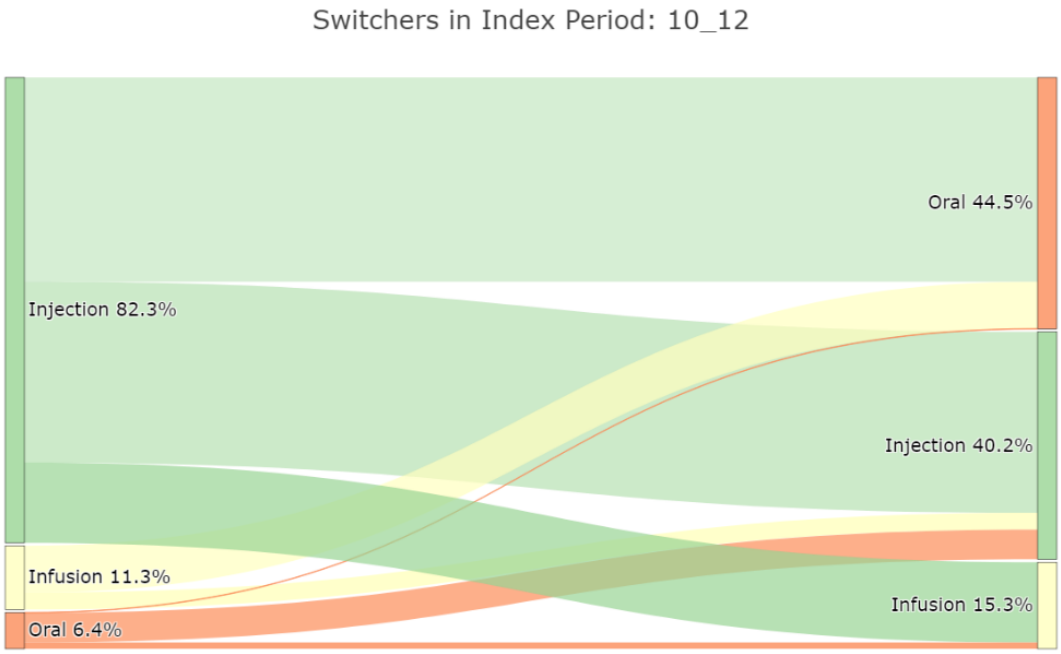
C.


Time to Discontinuation - Orals
Proportion of Patients on DMT
1.0
0.9
0.8
0.7
0.6
0.5
0.4
10_12
13_15
16_18
0
6
12
18
24
30
36
Month
Patients
2229 1918 1498 1062 701 398 197
3285 2841 2613 2401 2188 2014 1848
860 769 706 665 644 616 559

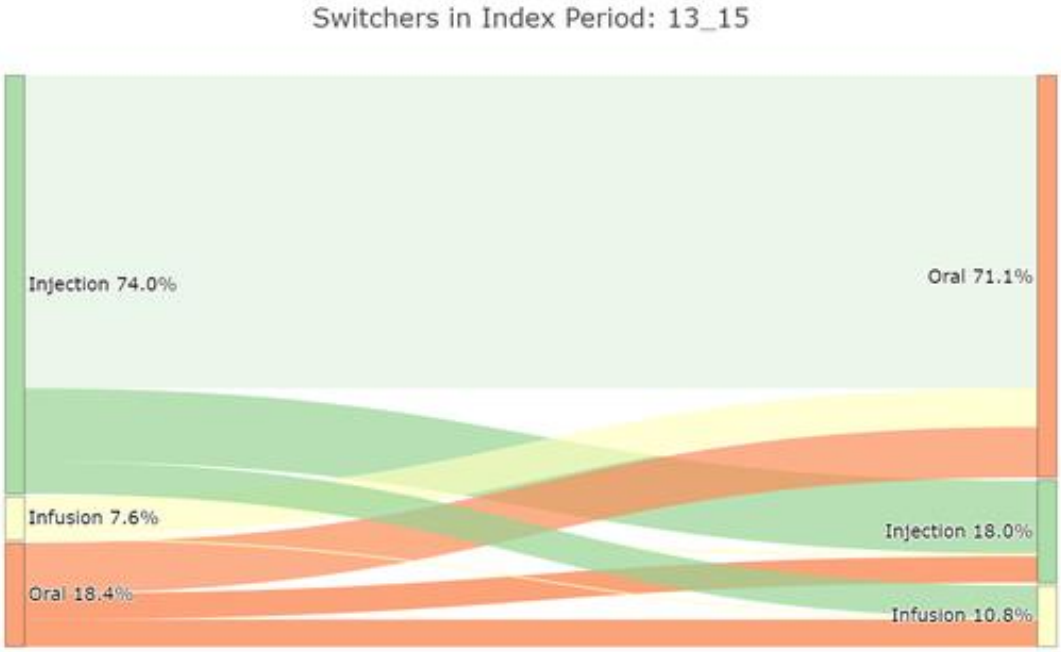
D.


Time to Discontinuation - Infusion
Proportion of Patients on DMT
1.0
0.9
0.8
0.7
0.6
0.5
0.4
10_12
13_15
16_18
0
6
12
18
24
30
36
Month
Patients
404 375 321 237 164 102 51
393 359 327 303 269 244 229
342 307 283 243 208 172 139

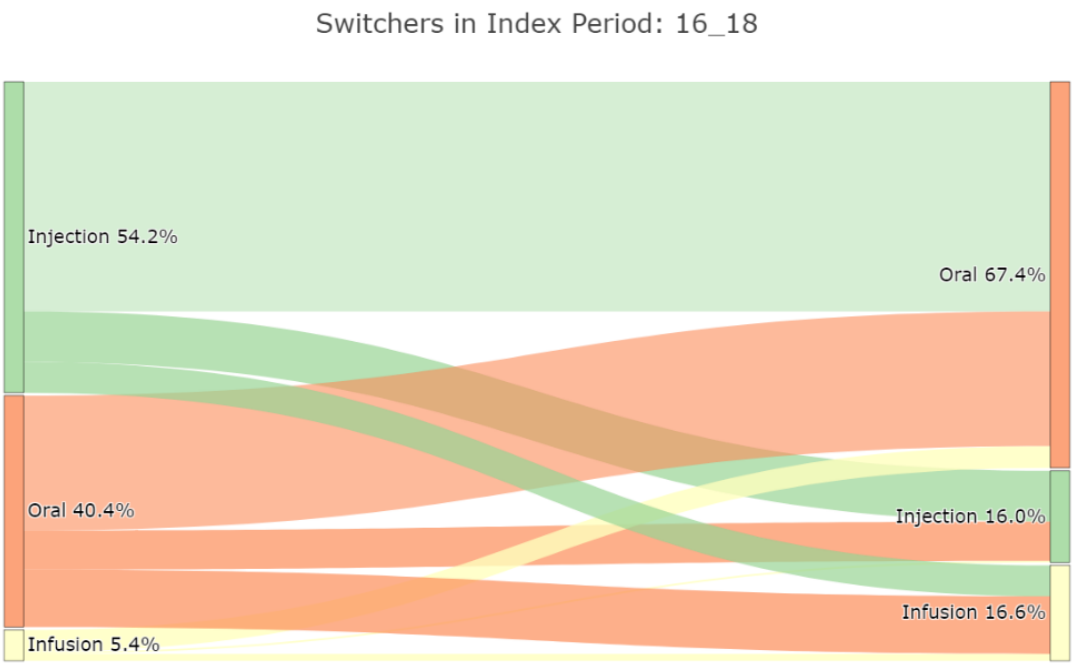
A.

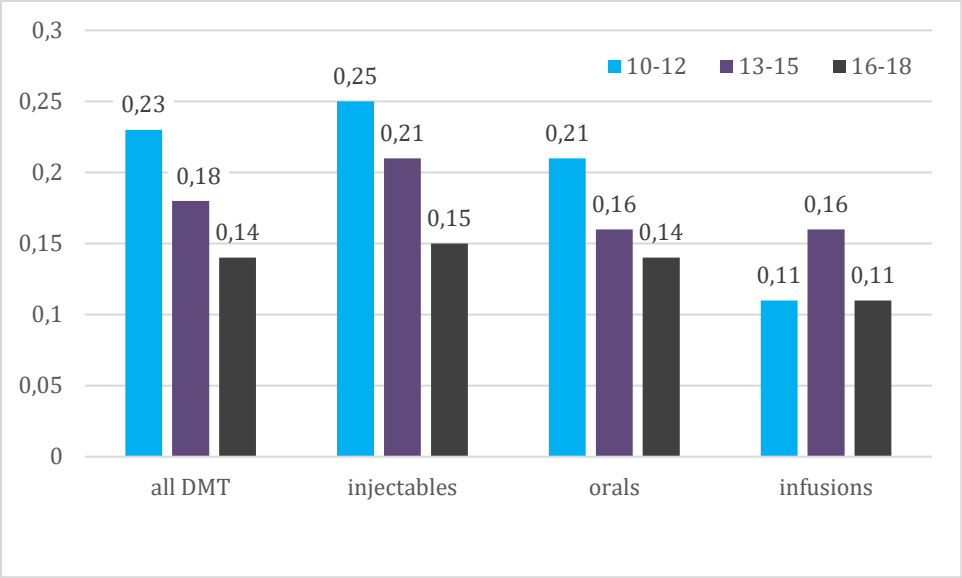

Switchers in Index Period: 10_12
Injection 82.3%
Infusion 11.3%
Oral 6.4%
Oral 44.5%
Injection 40.2%
Infusion 15.3%

B.


Switchers in Index Period: 13_15
Injection 74.0%
Infusion 7.6%
Oral 18.4%
Oral 71.1%
Injection 18.0%
Infusion 10.8%

C.





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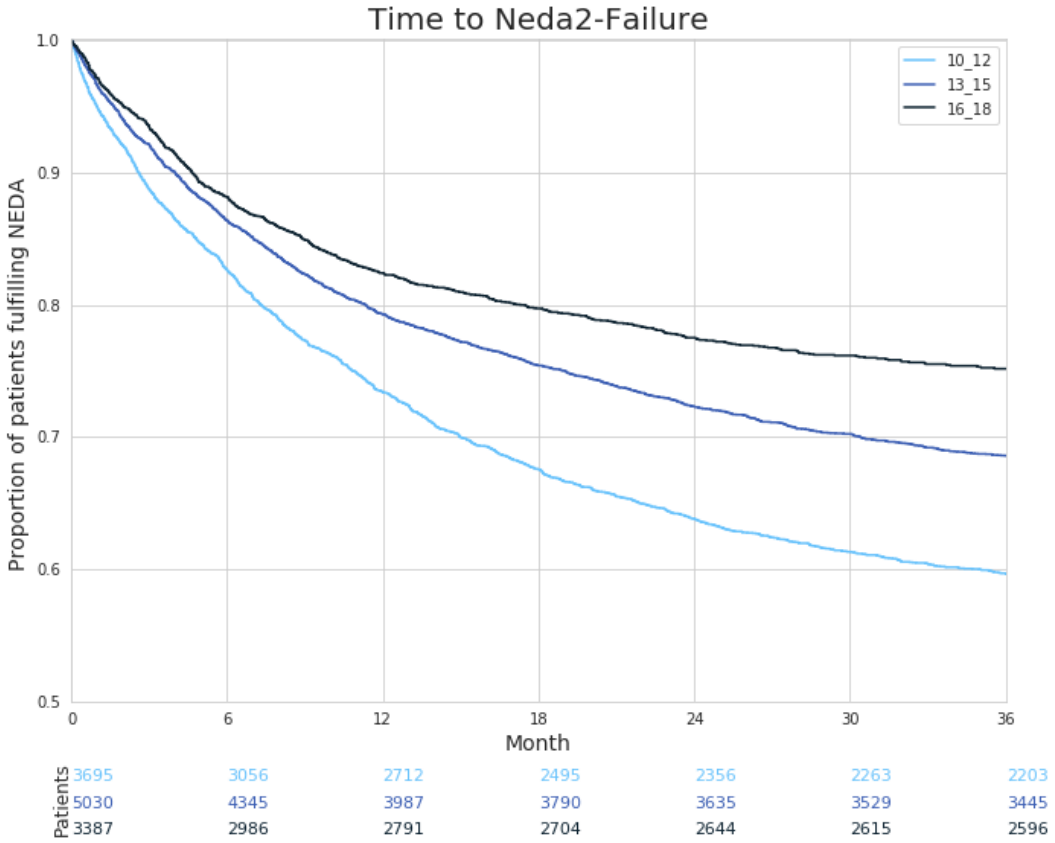
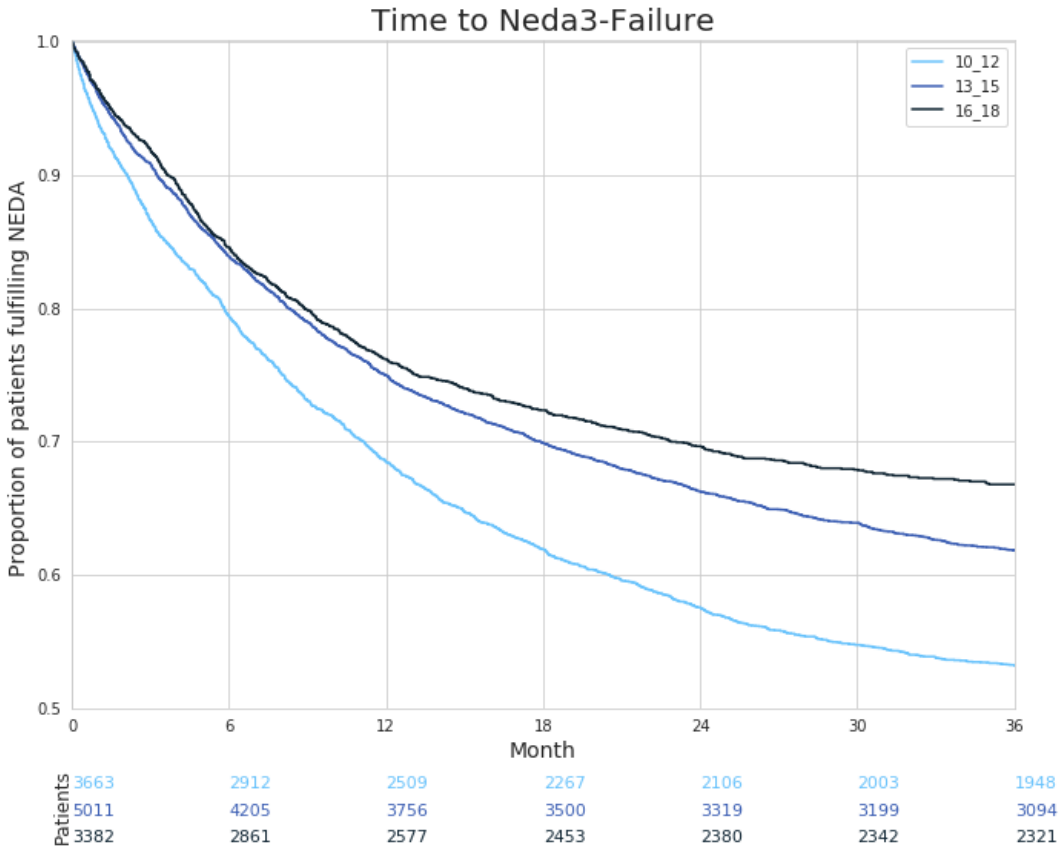

Time to Neda2-Failure
Proportion of patients fulfilling NEDA
1.0
0.9
0.8
0.7
0.6
0.5
0
6
12
18
24
30
36
Month
10_12
13_15
16_18
Patients
3695 3056 2712 2495 2356 2263 2203
5030 4345 3987 3790 3635 3529 3445
3387 2986 2791 2704 2644 2615 2596

B.


Time to Neda3-Failure
Proportion of patients fulfilling NEDA
1.0
0.9
0.8
0.7
0.6
0.5
0
6
12
18
24
30
36
Month
10_12
13_15
16_18
Patients
3663 2912 2509 2267 2106 2003 1948
5011 4205 3756 3500 3319 3199 3094
3382 2861 2577 2453 2380 2342 2321

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	☺
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	☺
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	☺
Objectives	3	State specific objectives, including any prespecified hypotheses	☺
Methods			
Study design	4	Present key elements of study design early in the paper	☺
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	☺
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	☺
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	☺
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	☺
Bias	9	Describe any efforts to address potential sources of bias	☺
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	☺
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	☺
		(*b*) Describe any methods used to examine subgroups and interactions	☺
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	☺
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	☺
		(b) Indicate number of participants with missing data for each variable of interest	☺
		(c) Summarise follow-up time (eg, average and total amount)	☺
Outcome data	15*	Report numbers of outcome events or summary measures over time	☺
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which	NA

		confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	☺
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	☺
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	☺
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	☺
Generalisability	21	Discuss the generalisability (external validity) of the study results	NA
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	☺

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

The impact of drug diversity on treatment effectiveness in relapsing-remitting multiple sclerosis (RRMS) in Germany between 2010 and 2018: real-world data from the German NeuroTransData Multiple sclerosis registry

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Secondary Subject Heading:	Health services research, Patient-centred medicine, Qualitative research
Keywords:	THERAPEUTICS, Adult neurology < NEUROLOGY, NEUROLOGY, Multiple sclerosis < NEUROLOGY

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The impact of drug diversity on treatment effectiveness in relapsing-remitting multiple sclerosis (RRMS) in Germany between 2010 and 2018: real-world data from the German NeuroTransData Multiple sclerosis registry

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NTD Study Group, Doctors and study nurses of the German NeuroTransData network, see www.neurotransdata.com/praxen

Abstract

Objective

To evaluate the impact of drug diversity on treatment effectiveness in relapsing-remitting multiple sclerosis (RRMS) in Germany.

Design

This study employs real world data captured in-time during clinical visits in 67 German neurology outpatient offices of the NeuroTransData (NTD) MS registry between 1 Jan 2010 and 30 Jun 2019, including 237,976 visits of 17,553 RRMS patients. Adherence and clinical effectiveness parameters were analyzed by descriptive statistics, time-to-event analysis overall and by disease modifying therapies (DMTs) stratified by administration modes (injectable, oral and infusion). Three time periods were compared: 2010–2012, 2013–2015, and 2016–2018.

Results

Between 2010 and 2018, an increasing proportion of RRMS patients were treated with DMTs and treatment was initiated sooner after diagnosis of MS. Introduction of oral DMT temporarily induced higher readiness to switch. Comparing the three index periods, there was a continuous decrease of annualized relapse rates, less frequent EDSS progression and increasing periods without relapse, EDSS worsening and with stability of no-evidence-of-disease-activity (NEDA) 2 and 3 criteria, lower conversion rates to secondary progressive MS (SPMS) on oral and on injectable DMTs.

Conclusion

Sparked by the availability of new mainly oral DMTs, RRMS treatment effectiveness improved clinically meaningful between 2010 and 2018. As similar effects were seen for injectable and oral DMTs more than for infusions, a better personalized treatment allocation in many patients is likely. These results indicate that there is an overall beneficial effect for the whole MS patient population as a result of the greater selection of available DMTs, a benefit beyond the head-to-head comparative efficacy, resulting from an increased probability and readiness to individualize MS therapy.

Strengths and limitations

The strengths of our study include its sustained high population size, constant high frequency of visits per year documented and mean duration of follow up of 5.07 years (SD 4.46), the consistency of formats and definitions of the data over the whole study period between 2010 until 2019, the high level of data completeness of the MS core data set as recommended by the European medical agency (EMA/548474/2017) and high data accuracy accomplished by multiple data quality steps from automated data entry checks to regular data consistency checks every 3 months and requests for missing

information. Analysis was performed without data imputation. Limitations are the inclusion of outpatients only and of only German MS patients. Follow-up times varied between patients. As there is no validated, generally accepted definition of SPMS, the diagnosis of SPMS is made by clinical judgement of the treating physician based on best medical knowledge. Also the time of clinical diagnosis of RRMS and SPMS are not reflecting their true pathophysiological start, which has to be accepted as best possible standard. Like all observational studies, residual confounding by unknown confounders is possible.

Introduction

The field of multiple sclerosis (MS) treatment have seen dynamic developments over the last three decades. 1. Since the introduction of the first interferon-β1a (IF-b1a) in 1994, treatment options for patients with relapsing remitting MS (RRMS) have expanded to 14 different disease modifying therapies (DMTs) registered in Europe. 2. Regulatory authorities have defined new MS subgroups such as high-disease activity course of RRMS, relapsing MS (RMS), RRMS and relapsing forms of secondary progressive MS, for the definition of drug labels 3. Regulatory authorities have also developed legislative and administrative initiatives such as the "AMNOG procedure" to control costs of drugs, in the face of drug costs in Germany raising from €30.2 billion to €43.9 billion from 2010–2018.[1] 4. Patients, physicians and payers expect allocation of the most effective DMT for the individual patient while minimizing adverse events. While reduction of relapse activity was the treatment goal in the 1990s, current treatment goals strive for "no evidence of disease activity".

However, little is known about the impact of these developments on real-world treatment pattern and effectiveness on disease activity in RRMS. This analysis investigates treatment pattern and effectiveness over time by comparing three time periods between 2010 and 2018 (defined by availability of new DMTs entering the German market) of real-world data from the physician´s network NeuroTransData (NTD) in Germany.

Methods

Database: the NTD multiple sclerosis registry

This project employed real-world clinical data captured by the NeuroTransData (NTD) multiple sclerosis registry. NTD is a Germany-wide physicians´ network founded in 2008 and run by physicians in the fields of neurology and psychiatry (www.neurotransdata.com). Governance principles are defined. NTD generates revenue by its members' participation in phase II–IV clinical trials, investigator initiated trials,

and real-world data analytic projects in cooperation with pharmaceutical industry, payers and other players in the German and international health systems.

Currently, 132 specialists work in 67 NTD practices throughout Germany, serving approximately 600,000 outpatients per year. Each practice is certified according to network-specific and ISO 9001 criteria. An external certified organization audits compliance annually. The NTD MS registry includes approximately 25,000 patients with MS, representing about 15% of all MS patients in Germany. NTD captures demographic, clinical history, patient-related outcomes, and clinical variables in real time during clinical visits. Standardized clinical assessments of functional system scores and EDSS calculation are performed by certified raters (http://www.neurostatus.net). Data are entered into the web-based registry either manually or directly from digital sources. Data quality is monitored by the NTD data management team, checking for inconsistencies and errors using an error analysis program. Both automatic and manually executed queries are implemented to further ensure data quality, e.g. checks for inconsistencies and requests for missing information. High data completeness is achieved by definition of minimum data sets, mandatory data entry fields, positive missing data confirmation. Advanced dynamic web-based data capturing, regular training of doctors and nurses, interactive chat forum for nurses and doctors, automated and manual feedback query system, daily-automated analysis of data plausibility and correctness, and annual on-site audit of procedures and source data by an external process quality certifier organization contribute to high data consistency. The NTD data capturing platform is also used as patient management system in the daily care of patients in NTD offices, thus guaranteeing timeliness of data.

All data are pseudonymized and pooled. The Institute for Medical Information Processing, Biometry and Epidemiology (Institut für medizinische Informationsverarbeitung, Biometrie und Epidemiologie (IBE)) at the Ludwig Maximilian University in Munich, Germany, manages codes and acts as an external trust center. Pooled data are stored on NTD servers and other NTD-controlled storage technology. This data acquisition and management protocol was approved by the ethical committee of the Bavarian Medical Board (Bayerische Landesärztekammer, June 14, 2012) and re-approved by the ethical committee of the Medical Board North-Rhine (Ärztekammer Nordrhein, April 25, 2017). Compliance with European and German legislation (BDSG, EU-DSGVO) is warranted including patient rights and informed consent requirements. Patient participation, informed consent procedures, data capturing, management and analytics fulfill the “Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology”[2], the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[3], the European Medicines Agency requirements for the “Use of patient disease registries for regulatory purposes – methodological and operational considerations”[4] and the ethical principles laid down in the Declaration of Helsinki[5].

Data for this project were captured between 1 January 2010 and 30 June 2019.

Data quality of the NeuroTransData Multiple Sclerosis registry

The main components for data quality of medical real-world data registries proposed by European Medicine Agency[4] are fulfilled by the NTD MS registry. The NTD also realizes the quality criteria of the EunetHTA REQueST (Registry Evaluation and Quality Standards Tool)[6] with 14 of 14 points in section "Methodological Information", 23 of 24 points in section "Essential Standards" and 5 of 6 points in section "Additional Requirements".

Patient population

All patients with diagnosis of relapsing-remitting or secondary progressive multiple sclerosis documented in the NTD MS registry between 01.01.2010 and 30.12.2018 with at least one clinical visit were included. In patients with RRMS the McDonald criteria as defined at the time of diagnosis of MS had to be fulfilled and documented in the registry. 17,553 patients with RRMS were included.

From this population 12,181 RRMS patients were identified in whom a DMT was initiated between 2010 and 2018. This group was stratified in three populations according to their time of initiation of DMT (see next section).

As there is no accepted and validated diagnostic procedure to confirm SPMS, the generally applied diagnostic criteria for SPMS were applied by the treating neurologists to establish this diagnosis. Time of switch from RRMS to SPMS is defined as the first clinical visit, when in the treating neurologists´ judgement the criteria for manifest SPMS were fulfilled.

Data analysis

Analysis was performed in 3 time periods, reflecting different spectra of DMTs available during the respective period.

2010–2012 (index period 10–12): era of early treatment initiation at the stage of clinically isolated syndrome (CIS) with interferons and glatiramer acetate and escalation with natalizumab approved since 2006 and fingolimod approved since 2011 for high-disease-activity (HDA) patients. HDA is defined by the European Medicines Agency drug label as active disease despite treatment with at least one disease modifying therapy or disease activity with 2 or more disabling relapses in one year without therapy, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

2013–2015 (index period 13–15): era of therapy diversification with introduction of alemtuzumab as an infusion for HDA patients, teriflunomide and dimethyl fumarate as oral drugs for all stages of RRMS.

2016–2018 (index period 16–18): era of consolidated DMT spectrum. Cladribine, an oral HDA activity drug, was newly approved in August 2017. Daclizumab, which became available in July 2016, was restricted in July 2017 and withdrawn in March 2018, was not considered as numbers of patients were very small and a temporary distortion of results in the injectable group had to be excluded.

Parameters characterizing treatment acceptance and adherence were analysed for each index period.

Impact on treatment effectiveness was analyzed between 2010 and 2018 and for each index period for the strata "all DMT", "injectables" including interferons-ß-1a, interferons-ß-1b, glatiramer acetate, "orals" including fingolimod, teriflunomide, dimethyl fumarate, cladribine, "infusions" including natalizumab, alemtuzumab, based on the European labels of these DMTs.

Treatment effectiveness was analysed for RRMS patients on DMT by annualized relapse rate (ARR), time-to-first-relapse on DMT, percentage of patients with 6 months confirmed disability-progression (6mCDP, CDP defined as at least 1.0-point EDSS score increases for patients with baseline EDSS score 0–5.5 EDSS and at least 0.5-point EDSS score increases for patients with baseline EDSS score greater than 5.5), time-to-6mCDP on DMT, time-from-first symptom to EDSS >=3-5 and >5 (in month), time-to-no-evidence-of-disease-activity (NEDA) 2 and 3 failure on DMT being started in the index periods. NEDA 2 is defined as no clinical evidence of relapse activity or disability progression. For NEDA 3 status no evidence of MRI activity, either new lesions or Gadolinium enhancing lesions, is required in addition to NEDA 2 criteria. Risk rates for discontinuation were calculated as ratio of number of patients with discontinuation of DMT divided by all patients.

Patient and Public Involvement

There was no patient involvement.

Role of funding source

This study was conducted by NTD without additional funding or guidance by external sponsors.

Results

Data Quality

Exemplary frequencies of data captured constantly over time for several data items (see Table 1) underline the high data quality and consistency over time. The mean duration of follow-up was 5.07 years (SD 4.46). A total of 59,928 DMT treatment cycles were documented between 2010 and 2018.

Table 1. Numbers of patients with RRMS, visits per year and therapy cycles with DMTs captured in the NTD MS registry between 2010 and 2018. DMT, disease-modifying treatment; MRI, magnetic resonance imaging; RRMS, relapsing remitting multiple sclerosis.

Index year	Number RRMS patients	Visits documented per year	DMT cycles per year	Relapses per year	MRI per year
2010	5,170	16,377	4,168	1,821	3,096
2011	6,648	24,296	5,441	2,638	4,004
2012	7,017	23,298	5,893	2,600	3,107
2013	7,532	25,840	6,410	2,433	3,866
2014	7,591	28,261	7,536	2,076	3,989
2015	8,074	28,313	7,443	1,972	3,879
2016	8,401	29,715	7,566	1,795	3,781
2017	9,021	31,199	7,862	1,707	3,575
2018	8,946	30,677	7,609	1,487	4,102
2010–2018		237,976	59,928	18,529	33,399
Mean/patient/year		3.48	0.88	0.27	0.49

Patient Population

A total of 17,553 patients with RRMS were identified between 2010 and 2018 (73.6% female, 26.4% male). Mean age at diagnosis of RRMS was 34 years (SD 10.66), mean annualized relapse rate between 2010 and 2018 was 0.27 (SD 0.6). From this group, in 12.181 patients a DMT was initiated in this period. Table 2 shows consistency and

completeness of data of this patient group stratified into the three time periods between 2010 and 2018.

Table 2. Means and percentages of RRMS patient characteristics of the NTD MS registry in time periods between 2010 and 2018 at initiation of DMT (=index event). DMT, disease-modifying therapy MRI, magnetic resonance imaging; RRMS, relapsing remitting multiple sclerosis; SD, standard deviation.

Characteristic	10–12 (N=3,942)	13–15 (N=5,101)	16–18 (N=3,138)	All patients (N=12,181)
Female, %	73.17	73.74	71,86	73.07
Age, years (SD)	44.95 (10.21)	43.93 (10.88)	40.7 (11.03)	43.59 (10.94)
EDSS (SD)	2.12 (1.59)	2.10 (1.62)	1.89 (1.53)	2.05 (1.59)
Relapses (SD)before index event	1.93 (2.55)	2.26 (2.63)	2.21 (2.67)	2.14 (2.62)
Months MS duration (SD)	87.78 (85.87)	101.78 (93.62)	98.73 (94.99)	96.46 (91.75)
DMTs before index event (SD)	0.8 (1.01)	1.08 (1.14)	1.2 (1.26)	1.02 (1.14)
MRI around index event, %	39.93	43.5	37.38	40.77
MRI with progression around index event, %	20.83	20.78	18.36	20.17

Treatment acceptance

Overall proportions of RRMS patients actively treated with DMT increased steadily: 10–12, 70,7%; 13–15, 78.1%; 16–18, 80,1%. Proportions of DMT types by application changed during the 3 time periods 10–12/13–15/16–18 with percentages of patients on injectables 88/69/46, orals 13/44/54, infusions 12/10/10. Total percentages per period exceed 100% as some patients received more than one DMT per period (see section "Persistence on DMT"). Proportions of RRMS patients receiving so-called high-disease activity DMTs increased continuously: 10–12, 23%; 13–15, 27%; 16–18, 31%.

Initiation of DMT after diagnosis of RRMS

More patients started on a DMT within 6 months after diagnosis of RRMS (10–12, 62%; 13–15, 72%; 16–17, 66%), with shorter periods between first symptom and initiation of first DMT (10–12, 178 ±295 days; 13–15, 121 ±174 days; 16–18, 115 ±112 days). Orals were increasingly preferred as first DMT as they became available during the 3 periods of time 10–12/13–15/16–18 with percentages of patients on injectables 74/44/40, orals 19/52/55, infusions 7/4/5.

Persistence on DMT

Availability of oral DMT increased the proportion of switches between DMTs from 16% of patients on treatment in 10–12 to 24% in 13–15, while in 16–18, 14% of patients on DMT switched. In parallel, time to discontinuation remained stable within these 3-years periods: in 10–12 mean time to discontinuation 8.49 months (SD 7.14); in 13–15, 8.10 months (SD 6.92); and in 16–18, 8.49 months (SD 7.71). There was a trend for patients staying longer on overall treatment for the most recent time period. This trend was driven by longer persistence of patients on infusion therapies in the most recent time period (Figure 1).

Figure 1. Time to discontinuation of DMTs in RRMS patients for time periods 2010–2012, 2013–2015, 2016–2018, all DMT (A) and by injectables (B), orals (C), infusions (D). DMT, disease-modifying treatments; RRMS, relapsing remitting multiple sclerosis

A. all DMT

B Injectables

C Orals

D Infusions

Non-medical reasons for discontinuation, such as patients´ perceptions and wishes, decreased over time from 71 to 51%. Lack of effectiveness is increased as a motivation for switching DMTs, as well as adverse events or pregnancy/family planning (Table 3).

Table 3. Reasons overall and risk rates by application type of DMT for discontinuation for three time periods 2010–2012, 2013–2015, and 2016–2018.
Non-medical reasons summarize patients´ perceptions and wishes. DMT, disease-modifying treatment; NA, not applicable as criteria was not captured.

Reasons for discontinuation, %	**10–12**	**13–15**	**16–18**
Antibodies/JCV-virus titer	1.28	1.85	1.51
amily planning	4.10	5.48	6.34
Adverse events	5.13	15.89	13.12
Lack of effectiveness	18.21	19.31	27.90
Freedom of disease activity	NA	0.34	0.36
Non-medical reasons	71.28	57.11	50.76
Risk rates for discontinuation			
Injectables	0.59	0.54	0.33
Orals	0.39	0.36	0.21
Infusions	0.59	0.37	0.17

Risk rates for discontinuation decreased continuously for all types of DMT over the three time periods, reaching a decrease of 44% for injectables, 46% for orals and 71% for infusions between 2010–2012 and 2016–2018.

DMT switching pattern

Patients increasingly switched from injectables to oral infusion DMTs, while switches to injectables decreased. Follow-on DMTs after oral DMTs were predominantly oral DMT. If infusion therapy was discontinued, almost all patients continued with oral DMTs (see Figure 2).

Figure 2. Percentage of switches between injectable, oral and infusion DMTs in RRMS for time periods A) 2010–2012, B) 2013–2015, C) 2016–2018. DMT, disease-modifying therapy; RRMS, relapsing remitting multiple sclerosis.

A

B

C

Treatment effectiveness

Relapse activity

Annualized relapse rate (ARR) decreased by a mean 39% overall, 40% for injectables and 30% for orals. Infusion therapies did not decrease (Figure 3).

Figure 3: Annualized relapse rate in three time periods 2010–2012, 2013–2015, 2016–2018 on DMT overall and by application type. DMT, disease-modifying therapy.

Proportions of patients documented with 6mCDP, with progression of EDSS <3 to ≥3–5 as well as from EDSS <5 to ≥5 decreased by 39% and 23%, respectively, between the first and the last time period analyzed. In parallel, times from first symptom of RRMS to reach the defined EDSS ranges increased by 22% and 15% respectively (see Table 4).

Table 4. Six months confirmed disability progression (6m CDP. EDSS increase of ≥1.0 for patients from previous EDSS): proportion of patients reaching EDSS >=3 to 5, reaching EDSS >=5 and months from first symptom of RRMS to 6mCDP in these strata.

	EDSS <3 to ≥3–<5	**EDSS <5 to ≥5**	**Months to 6mCDP EDSS ≥3-5**		**Months to 6mCDP EDSS ≥5**	
	% patients	% patients	Mean	SD	Mean	SD
10–12	1.02	0.26	122.30	81.03	181.59	92.17
13–15	0.76	0.31	130.95	85.60	181.37	110.04
16–18	0.62	0.20	149.26	93.32	209.73	97.70
Difference from 10–12 to 16–18, %	-39	-23	+22		+15	

Maintenance of NEDA 2 and 3 criteria

There was a clear trend that patients who initated DMTs for a minimum of 3 months in these index periods remained more frequently and longer free of disease activity according to NEDA 2 (no relapse, no 6mCDP) and NEDA 3 (no relapse, no 6MCDP, no MRI progression) criteria over the three periods of time (Figure 4).

Figure 4. A. Time to failure of no-evidence-of disease-activity (NEDA) 2 (no relapse, no confirmed disability progression) and B. NEDA 3 (no relapse, no 6months confirmed disability progression, no MRI worsening) criteria in RRMS patients on DMTs after a minimum treatment period of 3 months with treatment initiation within three time periods 2010–2012, 2013–2015, 2016–2018. DMT, disease-modifying treatment; MRI, magnetic resonance imaging; RRMS, relapsing remitting multiple sclerosis.

A.

B.

Mean times to NEDA 2 and 3 failure, censored for the 3 time periods, increased continuously. NEDA 2: 10–12, 6.92 months (SD 6.66); 13 –15, 7.10 months (SD 6.55); 16–18, 7.43 months (SD 7.11). NEDA 3: 10–12, 6.70 months (SD 6.41); 13–15, 7.16 months (SD 6,42); 16–18, 7.49 months (SD 6.89).

Progression to SPMS

Between 2010 and 2018, overall 2.34% of 17,553 patients switched from RRMS to SPMS during a mean follow-up time of 5.31 years. The mean time from first symptom of MS to SPMS was 214 months (SD 113.77), almost 18 years. Time-to-SPMS progression analysis did not reveal time differences between the 3 index time periods (not shown here). There was a continuous trend towards lower numbers of patients switching to SPMS while on DMT for at least 12 months from 4.25% in 10–12, to 1.97% in 13–15, and to 1.46% in 16–18.

Discussion

Medical guidelines, regulatory processes and public discussion in Germany and other countries regarding clinical benefits, treatment strategies and drug pricing are often focused on results from the randomized controlled trial (RCT) with an active comparator and versus placebo that led to registration of the drug[7]. However, clinical usage in a broad natural spectrum of patients and the increasing complexity of treatment options are causing a knowledge gap that RCTs are unable to fill. Thus, qualified real-world-data (RWD) are increasingly employed to evaluate optimization of therapeutic strategies[8-11]. Translating DMT efficacy studies into evidence-based clinical practice by meta-analysis of 123 unique RRMS studies was extremely limited. One main limitations was the paucity of efficacy data beyond 3 years of treatment[12]. Other initiatives addressed methodological aspects of this efficacy–effectiveness gap between results of RCTs in selected patient groups and effectiveness in real-world usage[13]. This is the first study to address population effects of a series of newly introduced DMTs in RRMS on adherence and clinical effectiveness.

Transparent data quality is the key stone of any scientific project. The physician-owned NTD MS registry can demonstrate constant data density, including a mean of 3.5 patient visits documented over the last 9 years, based on a defined minimal dataset and high data quality. This was achieved by utilization of web-based in-time data capturing and continuous development of automated and manual quality assurance measures for capturing data from 8,000 to 9,000 RRMS outpatients per year in Germany.

Definition criteria of the three time periods chosen for this study are thought to reflect periods characterized by different sets of DMTs being available for the treatment of RRMS patients. Between 2010 and 2018 the broader spectrum, in particular of oral DMTs motivated more patients to initiate DMT treatment and start earlier after diagnosis of RRMS. Availability of oral DMTs temporarily increased switches between DMTs in the years after their introduction from 16% in 2010–2012 to 24% of patients on DMT in 2013–2015, with a decline back to 14% of patients switching between 2016 and 2018. This is also reflected in the time-to-discontinuation analysis, showing more frequent and quicker discontinuation of injectables in 2013–2015. Lack of effectiveness and adverse events may have gained in importance over time as reasons for discontinuation of DMT, mirroring increasing expectations of doctors and patients regarding benefit/risk of DMTs. Persistence on classes of DMTs after 3 years improved most noticeable for infusions in 2010–2012 moving from 50% to almost 80% in 2015–2018, injectables increasing from less than 10% to 60% and orals achieving stable persistence of about 72%. Risk rates for discontinuation decreased overall and for each application type.

Earlier initiation of treatment and more readiness to search for individual optimal therapy by switching between a greater diversity of drugs may have impacted treatment effectiveness. ARR decreased overall and for patients on injectables and orals approximately 30–40% between 2010–2012 and 2016–2018. However, there was no

change in ARR over time for infusions. Furthermore, worsening of disability could be controlled better in parallel. The proportion of patients with EDSS reaching total sum scores >3 and > 5 decreased by 39% and 23%, respectively, and times from diagnosis to the 6mCDPs increased by 22 and 15%, respectively, when comparing time periods 2010–2012 and 2016–2018.

Comparing treatment cycles initiated in these 3 time periods, these positive developments are also reflected by continuously increasing proportions of patients maintaining NEDA 2 and NEDA 3 criteria. In addition, proportions of patients on DMT switching from RRMS to SPMS decreased each time period, but mean times to SPMS from diagnosis of RRMS remained unchanged at 17.8 years, corresponding with previous published data with a conversion time to SPMS on active treatment of 16.8 years [14]. The potential risk reduction for SPMS conversion on a broad spectrum of DMTs will have to be reevaluated in more detail as longer observation times on the new therapies become available.

The parallel improvements of reduction in ARR and disability progression, longer maintenance of NEDA 2 and 3 status in all types of DMTs, independent of their application modes, indicate that the broader selection of DMTs enable a better individual disease control in RRMS. It can be reasonably assumed that the regulatory introduced definition of high-disease-activity-labels further supported a more stringent application of the therapeutic options available. As expected, better treatment is associated with longer persistence. The observation that more efficient therapies achieved lower relapse activity in parallel with slower disability progression and longer persistence on DMTs is in line with a previous MSBase registry-based report in smaller groups of RRMS patients with advanced EDSS scores between 3 and 6[15], as well as more recent data in earlier disease stages[16]. Beside the individual patient´s fate, this is of great socioeconomic relevance, as costs and utility in MS are highly correlated with disease severity[17] and progression inducing disease activity[18]. In contrast, continuing interferon-ß and glatiramer acetate therapy 10 years or longer without optimization of therapy in response to disease activity results in an inevitable, almost linear increase in mean EDSS[19].

This study demonstrates a clinically meaningful, population-based benefit resulting from the availability of a broader selection of DMTs over time. The introduction of oral DMTs sparked a dynamic development between 2013 and 2015 with temporarily higher proportions of DMT switches but also more readiness to initiate DMTs earlier after diagnosis of MS. The similar extent of improvement of effectiveness parameter for oral and injectable DMTs demonstrates that this population effect is based on a more effective personalized allocation in individual patients.

Overall, these results indicate that there is an overall beneficial effect for the whole MS patient population as a result of the greater selection of available DMTs, a benefit beyond the head-to-head comparative efficacy, resulting from an increased probability and readiness to individualize MS therapy. Nevertheless, the challenge in daily practice

is the quick identification of the individually most effective DMT at a given time during the course of MS, particularly in patients with persistent disease activity on their current DMT, especially regarding the immanent risk of developing SPMS. Promising techniques emerge based on biomarker like neurofilament light chain[20] or B-cell activity response[21] or real-world-data-based statistical predictive algorithms[22]. As treatment decisions are driven currently by European label definitions, national cost control regulations and perceptions of physicians and patients, personalized-data-based decision support is required to further improve individual care.

Contributorship statement

SB planned the study, analysis and wrote the manuscript. FR assisted the data analysis, interpretation of results and drafting of the manuscript. HD performed the statistical analysis and aided data interpretation. AB aided in interpreting the results and worked on the manuscript. NTD study group collected the data, performed data cleansing and data extraction from the NTD MS registry. All authors discussed the results and commented on the manuscript.

Competing interests

All authors declare that they have no competing interests.

Funding

This project was founded by the NeuroTransdata network itself without external resources.

Data sharing statement

This project used deidentified patient data, owned by the participating doctors and provided for use in the NeuroTransData MS registry. Data can be made available upon reasonable request.

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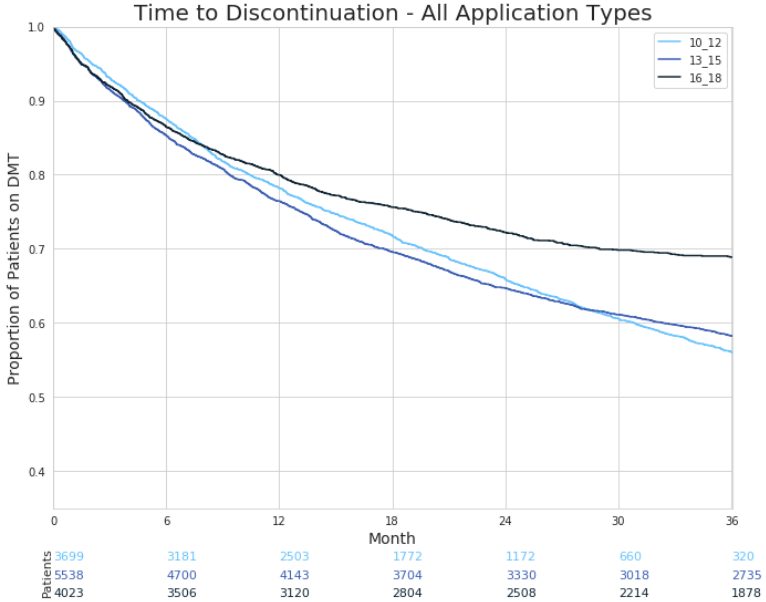
A.



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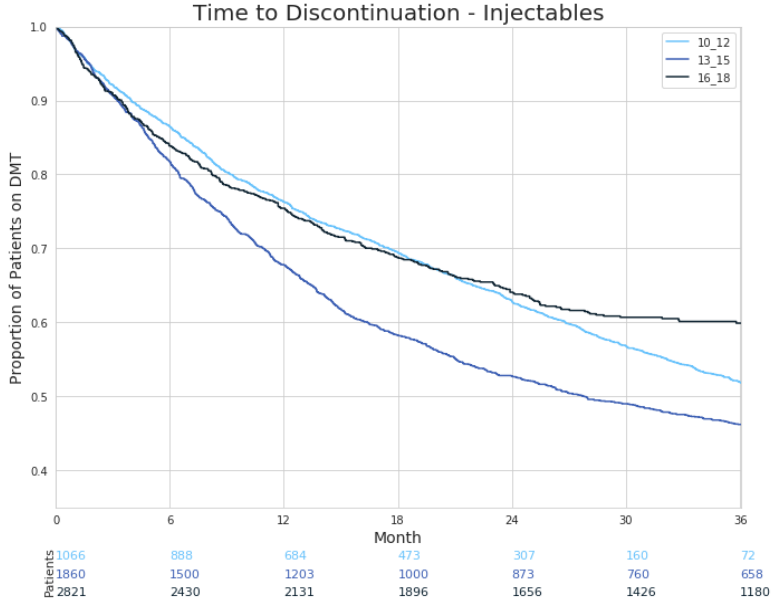

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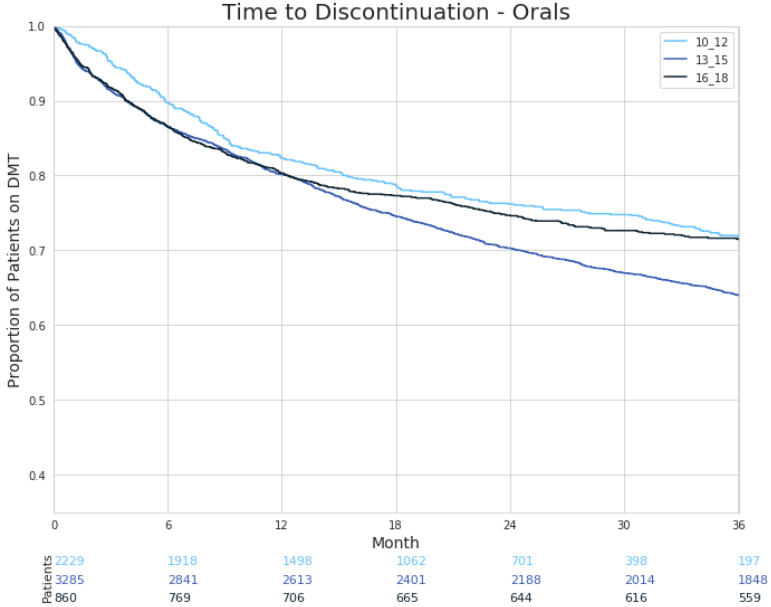

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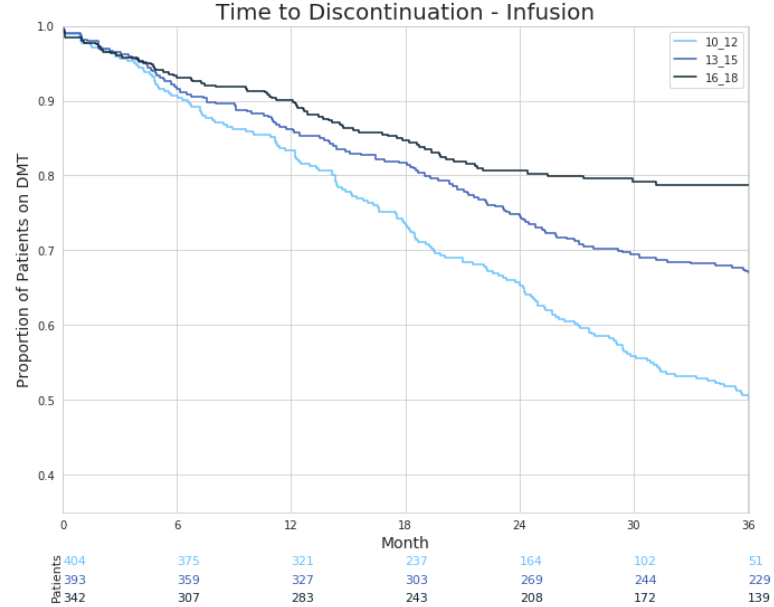

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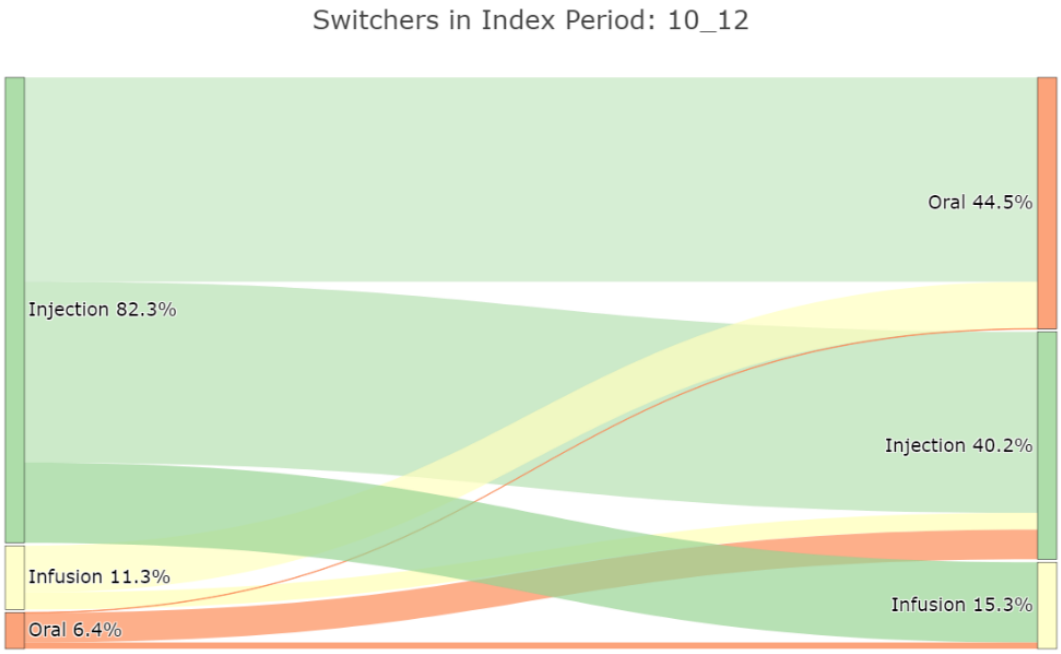
Switchers in Index Period: 10_12
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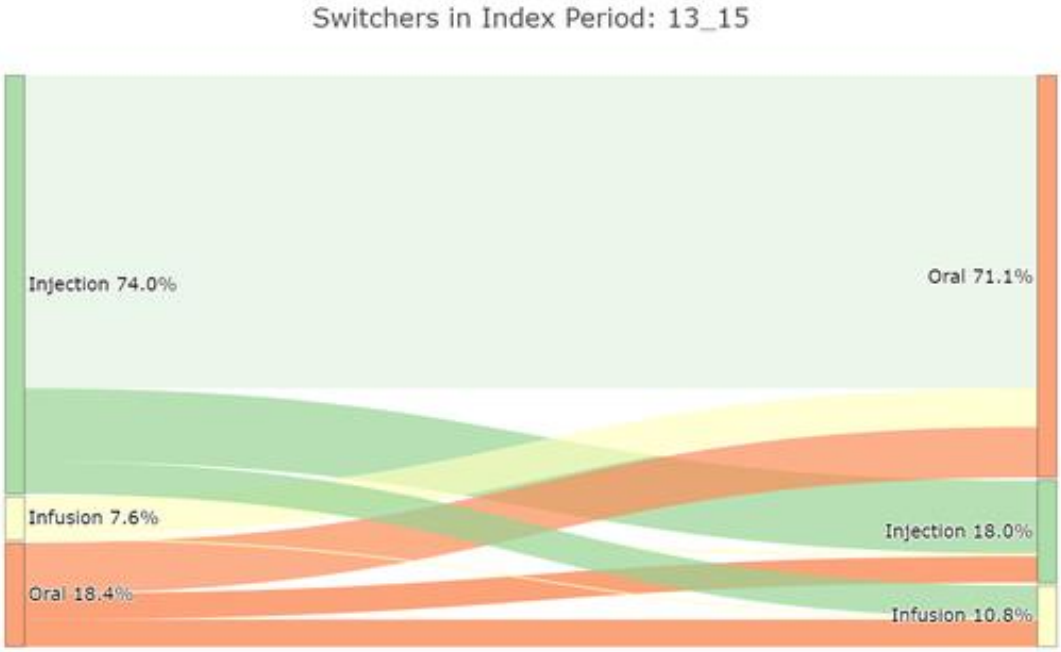
Infusion 11.3%
Oral 6.4%
Oral 44.5%
Injection 40.2%
Infusion 15.3%

B.


Switchers in Index Period: 13_15
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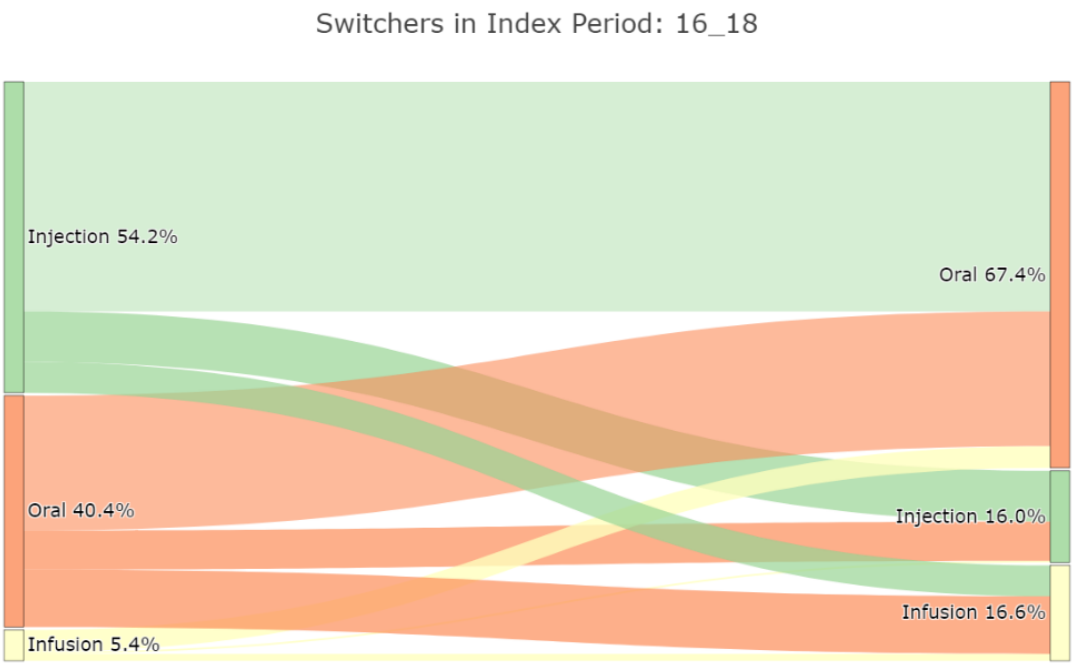
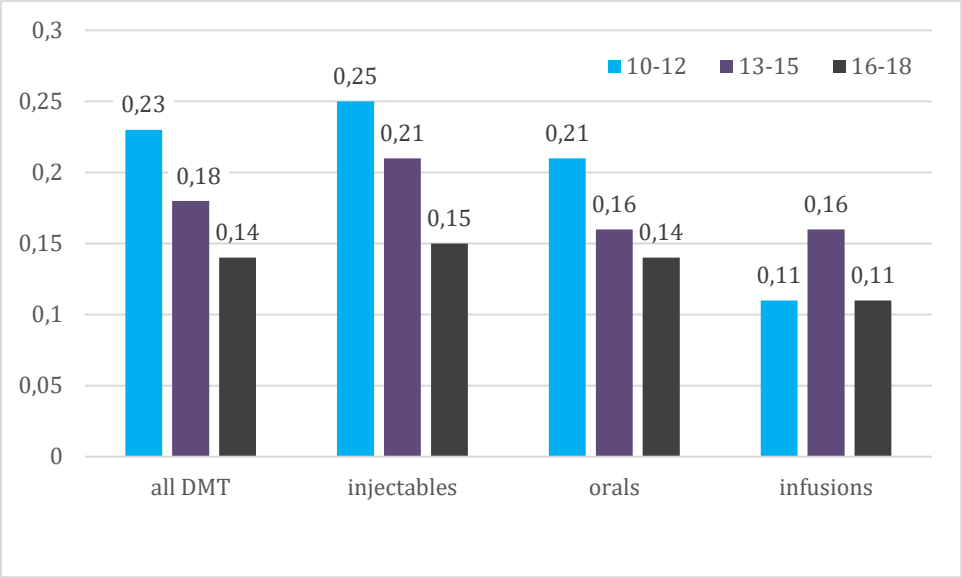
Oral 18.4%
Oral 71.1%
Injection 18.0%
Infusion 10.8%

C.





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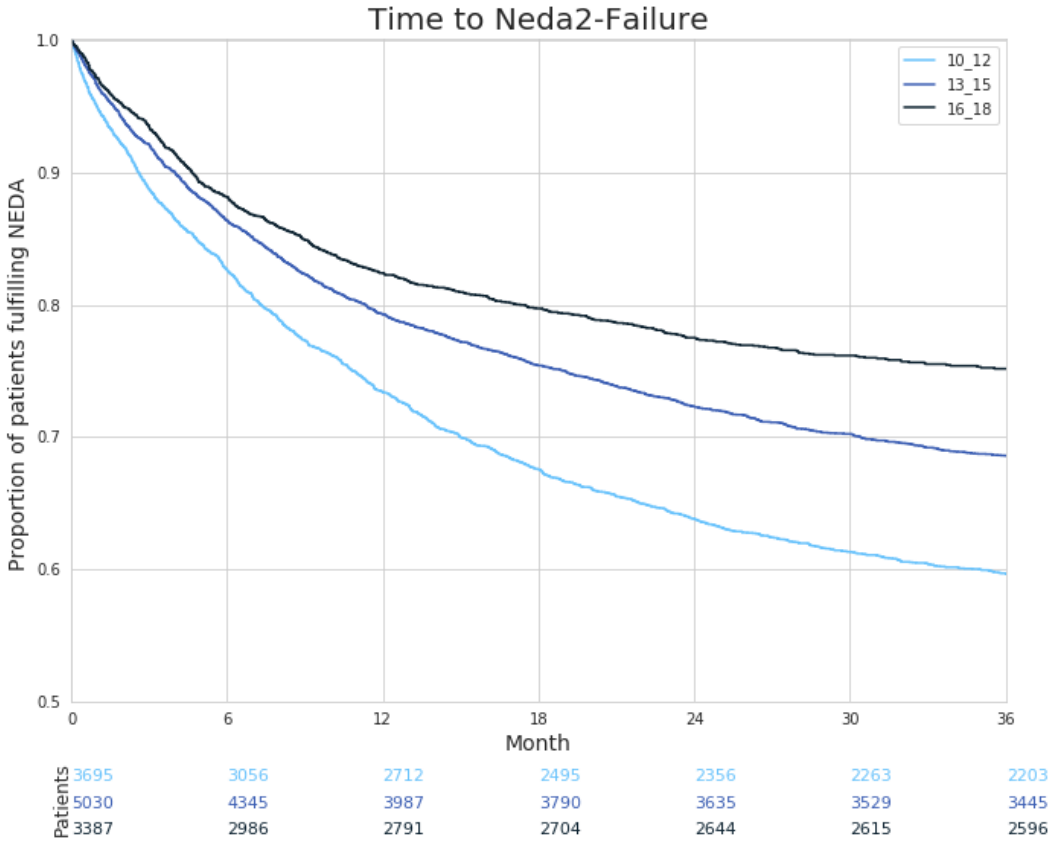
Time to Neda2-Failure
Proportion of patients fulfilling NEDA
1.0
0.9
0.8
0.7
0.6
0.5
0
6
12
18
24
30
36
Month
10_12
13_15
16_18
Patients
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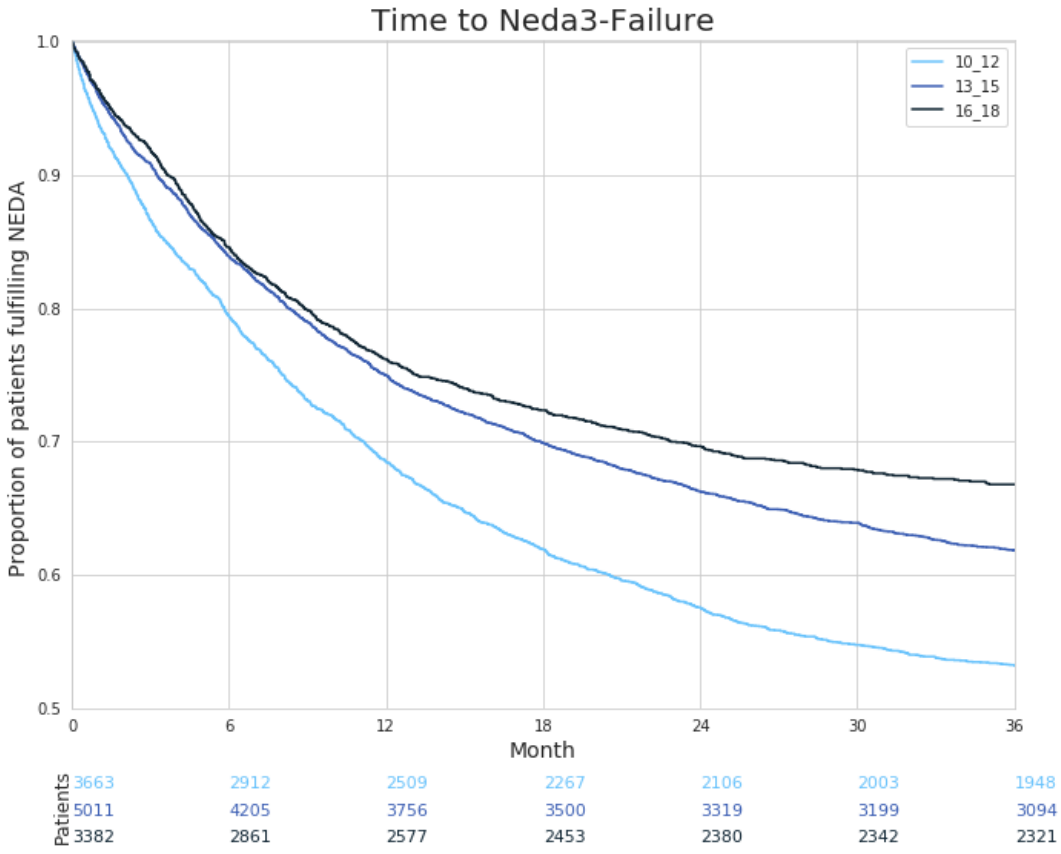
5030 4345 3987 3790 3635 3529 3445
3387 2986 2791 2704 2644 2615 2596

B.


Time to Neda3-Failure
Proportion of patients fulfilling NEDA
1.0
0.9
0.8
0.7
0.6
0.5
0
6
12
18
24
30
36
Month
10_12
13_15
16_18
Patients
3663 2912 2509 2267 2106 2003 1948
5011 4205 3756 3500 3319 3199 3094
3382 2861 2577 2453 2380 2342 2321

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	☺
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	☺
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	☺
Objectives	3	State specific objectives, including any prespecified hypotheses	☺
Methods			
Study design	4	Present key elements of study design early in the paper	☺
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	☺
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	☺
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	☺
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	☺
Bias	9	Describe any efforts to address potential sources of bias	☺
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	☺
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	☺
		(*b*) Describe any methods used to examine subgroups and interactions	☺
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	☺
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	☺
		(b) Indicate number of participants with missing data for each variable of interest	☺
		(c) Summarise follow-up time (eg, average and total amount)	☺
Outcome data	15*	Report numbers of outcome events or summary measures over time	☺
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which	NA

		confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	☺
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	☺
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	☺
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	☺
Generalisability	21	Discuss the generalisability (external validity) of the study results	NA
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	☺

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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The impact of drug diversity on treatment effectiveness in relapsing-remitting multiple sclerosis (RRMS) in Germany between 2010 and 2018: real-world data from the German NeuroTransData Multiple sclerosis registry

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Abstract

Objective

To evaluate the impact of drug diversity on treatment effectiveness in relapsing-remitting multiple sclerosis (RRMS) in Germany.

Design

This study employs real world data captured in-time during clinical visits in 67 German neurology outpatient offices of the NeuroTransData (NTD) MS registry between 1 Jan 2010 and 30 Jun 2019, including 237,976 visits of 17,553 RRMS patients. Adherence and clinical effectiveness parameters were analyzed by descriptive statistics, time-to-event analysis overall and by disease modifying therapies (DMTs) stratified by administration modes (injectable, oral and infusion). Three time periods were compared: 2010–2012, 2013–2015, and 2016–2018.

Results

Between 2010 and 2018, an increasing proportion of RRMS patients were treated with DMTs and treatment was initiated sooner after diagnosis of MS. Introduction of oral DMT temporarily induced higher readiness to switch. Comparing the three index periods, there was a continuous decrease of annualized relapse rates, less frequent EDSS progression and increasing periods without relapse, EDSS worsening and with stability of no-evidence-of-disease-activity (NEDA) 2 and 3 criteria, lower conversion rates to secondary progressive MS (SPMS) on oral and on injectable DMTs.

Conclusion

Sparked by the availability of new mainly oral DMTs, RRMS treatment effectiveness improved clinically meaningful between 2010 and 2018. As similar effects were seen for injectable and oral DMTs more than for infusions, a better personalized treatment allocation in many patients is likely. These results indicate that there is an overall beneficial effect for the whole MS patient population as a result of the greater selection of available DMTs, a benefit beyond the head-to-head comparative efficacy, resulting from an increased probability and readiness to individualize MS therapy.

Strengths and limitations

- The descriptive real world data study in patients with relapsing remitting multiple sclerosis (RRMS) evaluates overall effects of the increasing number of disease modifying therapies (DMTs) in multiple sclerosis (MS) on quality of clinical care between 2010 and 2018 in Germany
- Pseudonymized data of the German NeuroTransData registry are employed including the MS core data set as recommended by the European medical agency (EMA/548474/2017)

- Sufficient patient numbers, high frequency of visits, standardized webbased data capturing by trained staff, consistency of formats and definitions of the data over the study period and multiple data quality assurance steps mitigate the risks of errors and biases.
- Limitations to the study are the inclusion of only German RRMS outpatients, application of German DMT labels and regulatory specifications, varying follow-up times, immanent uncertainties of the exact time when RRMS switches into secondary progressive MS (SPMS) and the risk of residual confounding of the results by unknown confounders.

Introduction

The field of multiple sclerosis (MS) treatment have seen dynamic developments over the last three decades. 1. Since the introduction of the first interferon-β1a (IF-b1a) in 1994, treatment options for patients with relapsing remitting MS (RRMS) have expanded to 14 different disease modifying therapies (DMTs) registered in Europe. 2. Regulatory authorities have defined new MS subgroups such as high-disease activity course of RRMS, relapsing MS (RMS), RRMS and relapsing forms of secondary progressive MS, for the definition of drug labels 3. Regulatory authorities have also developed legislative and administrative initiatives such as the "AMNOG procedure" to control costs of drugs, in the face of drug costs in Germany raising from €30.2 billion to €43.9 billion from 2010–2018.[1] 4. Patients, physicians and payers expect allocation of the most effective DMT for the individual patient while minimizing adverse events. While reduction of relapse activity was the treatment goal in the 1990s, current treatment goals strive for "no evidence of disease activity".

However, little is known about the impact of these developments on real-world treatment pattern and effectiveness on disease activity in RRMS. This analysis investigates treatment pattern and effectiveness over time by comparing three time periods between 2010 and 2018 (defined by availability of new DMTs entering the German market) of real-world data from the physician´s network NeuroTransData (NTD) in Germany.

Methods

Database: the NTD multiple sclerosis registry

This project employed real-world clinical data captured by the NeuroTransData (NTD) multiple sclerosis registry. NTD is a Germany-wide physicians´ network founded in 2008 and run by physicians in the fields of neurology and psychiatry (www.neurotransdata.com). Governance principles are defined. NTD generates revenue by its members' participation in phase II–IV clinical trials, investigator initiated trials,

and real-world data analytic projects in cooperation with pharmaceutical industry, payers and other players in the German and international health systems.

Currently, 132 specialists work in 67 NTD practices throughout Germany, serving approximately 600,000 outpatients per year. Each practice is certified according to network-specific and ISO 9001 criteria. An external certified organization audits compliance annually. The NTD MS registry includes approximately 25,000 patients with MS, representing about 15% of all MS patients in Germany. NTD captures demographic, clinical history, patient-related outcomes, and clinical variables in real time during clinical visits. Standardized clinical assessments of functional system scores and EDSS calculation are performed by certified raters (http://www.neurostatus.net). Data are entered into the web-based registry either manually or directly from digital sources. Data quality is monitored by the NTD data management team, checking for inconsistencies and errors using an error analysis program. Both automatic and manually executed queries are implemented to further ensure data quality, e.g. checks for inconsistencies and requests for missing information. High data completeness is achieved by definition of minimum data sets, mandatory data entry fields, positive missing data confirmation. Advanced dynamic web-based data capturing, regular training of doctors and nurses, interactive chat forum for nurses and doctors, automated and manual feedback query system, daily-automated analysis of data plausibility and correctness, and annual on-site audit of procedures and source data by an external process quality certifier organization contribute to high data consistency. The NTD data capturing platform is also used as patient management system in the daily care of patients in NTD offices, thus guaranteeing timeliness of data.

All data are pseudonymized and pooled. The Institute for Medical Information Processing, Biometry and Epidemiology (Institut für medizinische Informationsverarbeitung, Biometrie und Epidemiologie (IBE)) at the Ludwig Maximilian University in Munich, Germany, manages codes and acts as an external trust center. Pooled data are stored on NTD servers and other NTD-controlled storage technology. Written informed consent is obtained from each patient contributing data for the registry. This data acquisition and management protocol was approved by the ethical committee of the Bavarian Medical Board (Bayerische Landesärztekammer, June 14, 2012, ID 11144) and re-approved by the ethical committee of the Medical Board North-Rhine (Ärztekammer Nordrhein, April 25, 2017, ID 2017071). Compliance with European and German legislation (BDSG, EU-DSGVO) is warranted including patient rights and informed consent requirements. Patient participation, informed consent procedures, data capturing, management and analytics fulfill the “Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology”[2], the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[3], the European Medicines Agency requirements for the “Use of patient disease registries for regulatory purposes – methodological and operational considerations”[4] and the ethical principles laid down in the Declaration of Helsinki[5].

Data for this project were captured between 1 January 2010 and 30 June 2019.

Data quality of the NeuroTransData Multiple Sclerosis registry

The main components for data quality of medical real-world data registries proposed by European Medicine Agency[4] are fulfilled by the NTD MS registry. The NTD also realizes the quality criteria of the EunetHTA REQueST (Registry Evaluation and Quality Standards Tool)[6] with 14 of 14 points in section "Methodological Information", 23 of 24 points in section "Essential Standards" and 5 of 6 points in section "Additional Requirements".

Patient population

All patients with diagnosis of relapsing-remitting or secondary progressive multiple sclerosis documented in the NTD MS registry between 01.01.2010 and 30.12.2018 with at least one clinical visit were included. In patients with RRMS the McDonald criteria as defined at the time of diagnosis of MS had to be fulfilled and documented in the registry. 17,553 patients with RRMS were included.

From this population 12,181 RRMS patients were identified in whom a DMT was initiated between 2010 and 2018. This group was stratified in three populations according to their time of initiation of DMT (see next section).

As there is no accepted and validated diagnostic procedure to confirm SPMS, the generally applied diagnostic criteria for SPMS were applied by the treating neurologists to establish this diagnosis. Time of switch from RRMS to SPMS is defined as the first clinical visit, when in the treating neurologists´ judgement the criteria for manifest SPMS were fulfilled.

Data analysis

Analysis was performed in 3 time periods, reflecting different spectra of DMTs available during the respective period.

2010–2012 (index period 10–12): era of early treatment initiation at the stage of clinically isolated syndrome (CIS) with interferons and glatiramer acetate and escalation with natalizumab approved since 2006 and fingolimod approved since 2011 for high-disease-activity (HDA) patients. HDA is defined by the European Medicines Agency drug label as active disease despite treatment with at least one disease modifying therapy or disease activity with 2 or more disabling relapses in one year without therapy, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

2013–2015 (index period 13–15): era of therapy diversification with introduction of alemtuzumab as an infusion for HDA patients, teriflunomide and dimethyl fumarate as oral drugs for all stages of RRMS.

2016–2018 (index period 16–18): era of consolidated DMT spectrum. Cladribine, an oral HDA activity drug, was newly approved in August 2017. Daclizumab, which became available in July 2016, was restricted in July 2017 and withdrawn in March 2018, was not considered as numbers of patients were very small and a temporary distortion of results in the injectable group had to be excluded.

Parameters characterizing treatment acceptance and adherence were analysed for each index period.

Impact on treatment effectiveness was analyzed between 2010 and 2018 and for each index period for the strata "all DMT", "injectables" including interferons-ß-1a, interferons-ß-1b, glatiramer acetate, "orals" including fingolimod, teriflunomide, dimethyl fumarate, cladribine, "infusions" including natalizumab, alemtuzumab, based on the European labels of these DMTs.

Treatment effectiveness was analysed for RRMS patients on DMT by annualized relapse rate (ARR), time-to-first-relapse on DMT, percentage of patients with 6 months confirmed disability-progression (6mCDP, CDP defined as at least 1.0-point EDSS score increases for patients with baseline EDSS score 0–5.5 EDSS and at least 0.5-point EDSS score increases for patients with baseline EDSS score greater than 5.5), time-to-6mCDP on DMT, time-from-first symptom to EDSS >=3-5 and >5 (in month), time-to-no-evidence-of-disease-activity (NEDA) 2 and 3 failure on DMT being started in the index periods. NEDA 2 is defined as no clinical evidence of relapse activity or disability progression. For NEDA 3 status no evidence of MRI activity, either new lesions or Gadolinium enhancing lesions, is required in addition to NEDA 2 criteria. Risk rates for discontinuation were calculated as ratio of number of patients with discontinuation of DMT divided by all patients.

Patient and Public Involvement

There was no patient involvement.

Role of funding source

This study was conducted by NTD without additional funding or guidance by external sponsors.

Results

Data Quality

Exemplary frequencies of data captured constantly over time for several data items (see Table 1) underline the high data quality and consistency over time. The mean duration of follow-up was 5.07 years (SD 4.46). A total of 59,928 DMT treatment cycles were documented between 2010 and 2018.

Table 1. Numbers of patients with RRMS, visits per year and therapy cycles with DMTs captured in the NTD MS registry between 2010 and 2018. DMT, disease-modifying treatment; MRI, magnetic resonance imaging; RRMS, relapsing remitting multiple sclerosis.

Index year	Number RRMS patients	Visits documented per year	DMT cycles per year	Relapses per year	MRI per year
2010	5,170	16,377	4,168	1,821	3,096
2011	6,648	24,296	5,441	2,638	4,004
2012	7,017	23,298	5,893	2,600	3,107
2013	7,532	25,840	6,410	2,433	3,866
2014	7,591	28,261	7,536	2,076	3,989
2015	8,074	28,313	7,443	1,972	3,879
2016	8,401	29,715	7,566	1,795	3,781
2017	9,021	31,199	7,862	1,707	3,575
2018	8,946	30,677	7,609	1,487	4,102
2010–2018		237,976	59,928	18,529	33,399
Mean/patient/year		3.48	0.88	0.27	0.49

Patient Population

A total of 17,553 patients with RRMS were identified between 2010 and 2018 (73.6% female, 26.4% male). Mean age at diagnosis of RRMS was 34 years (SD 10.66), mean annualized relapse rate between 2010 and 2018 was 0.27 (SD 0.6). From this group, in 12.181 patients a DMT was initiated in this period. Table 2 shows consistency and

completeness of data of this patient group stratified into the three time periods between 2010 and 2018.

Table 2. Means and percentages of RRMS patient characteristics of the NTD MS registry in time periods between 2010 and 2018 at initiation of DMT (=index event). DMT, disease-modifying therapy MRI, magnetic resonance imaging; RRMS, relapsing remitting multiple sclerosis; SD, standard deviation.

Characteristic	10–12 (N=3,942)	13–15 (N=5,101)	16–18 (N=3,138)	All patients (N=12,181)
Female, %	73.17	73.74	71,86	73.07
Age, years (SD)	44.95 (10.21)	43.93 (10.88)	40.7 (11.03)	43.59 (10.94)
EDSS (SD)	2.12 (1.59)	2.10 (1.62)	1.89 (1.53)	2.05 (1.59)
Relapses (SD)before index event	1.93 (2.55)	2.26 (2.63)	2.21 (2.67)	2.14 (2.62)
Months MS duration (SD)	87.78 (85.87)	101.78 (93.62)	98.73 (94.99)	96.46 (91.75)
DMTs before index event (SD)	0.8 (1.01)	1.08 (1.14)	1.2 (1.26)	1.02 (1.14)
MRI around index event, %	39.93	43.5	37.38	40.77
MRI with progression around index event, %	20.83	20.78	18.36	20.17

Treatment acceptance

Overall proportions of RRMS patients actively treated with DMT increased steadily: 10–12, 70,7%; 13–15, 78.1%; 16–18, 80,1%. Proportions of DMT types by application changed during the 3 time periods 10–12/13–15/16–18 with percentages of patients on injectables 88/69/46, orals 13/44/54, infusions 12/10/10. Total percentages per period exceed 100% as some patients received more than one DMT per period (see section "Persistence on DMT"). Proportions of RRMS patients receiving so-called high-disease activity DMTs increased continuously: 10–12, 23%; 13–15, 27%; 16–18, 31%.

Initiation of DMT after diagnosis of RRMS

More patients started on a DMT within 6 months after diagnosis of RRMS (10–12, 62%; 13–15, 72%; 16–17, 66%), with shorter periods between first symptom and initiation of first DMT (10–12, 178 ±295 days; 13–15, 121 ±174 days; 16–18, 115 ±112 days). Orals were increasingly preferred as first DMT as they became available during the 3 periods of time 10–12/13–15/16–18 with percentages of patients on injectables 74/44/40, orals 19/52/55, infusions 7/4/5.

Persistence on DMT

Availability of oral DMT increased the proportion of switches between DMTs from 16% of patients on treatment in 10–12 to 24% in 13–15, while in 16–18, 14% of patients on DMT switched. In parallel, time to discontinuation remained stable within these 3-years periods: in 10–12 mean time to discontinuation 8.49 months (SD 7.14); in 13–15, 8.10 months (SD 6.92); and in 16–18, 8.49 months (SD 7.71). There was a trend for patients staying longer on overall treatment for the most recent time period. This trend was driven by longer persistence of patients on infusion therapies in the most recent time period (Figure 1).

Figure 1. Time to discontinuation of DMTs in RRMS patients for time periods 2010–2012, 2013–2015, 2016–2018, all DMT (A) and by injectables (B), orals (C), infusions (D). DMT, disease-modifying treatments; RRMS, relapsing remitting multiple sclerosis

A all DMT

B Injectables

C Orals

D Infusions

Non-medical reasons for discontinuation, such as patients´ perceptions and wishes, decreased over time from 71 to 51%. Lack of effectiveness is increased as a motivation for switching DMTs, as well as adverse events or pregnancy/family planning (Table 3).

Table 3. Reasons overall and risk rates by application type of DMT for discontinuation for three time periods 2010–2012, 2013–2015, and 2016–2018. Non-medical reasons summarize patients´ perceptions and wishes. DMT, disease-modifying treatment; NA, not applicable as criteria was not captured.

Reasons for discontinuation, %	**10–12**	**13–15**	**16–18**
Antibodies/JCV-virus titer	1.28	1.85	1.51
family planning	4.10	5.48	6.34
Adverse events	5.13	15.89	13.12
Lack of effectiveness	18.21	19.31	27.90
Freedom of disease activity	NA	0.34	0.36
Non-medical reasons	71.28	57.11	50.76
Risk rates for discontinuation			
Injectables	0.59	0.54	0.33
Orals	0.39	0.36	0.21
Infusions	0.59	0.37	0.17

Risk rates for discontinuation decreased continuously for all types of DMT over the three time periods, reaching a decrease of 44% for injectables, 46% for orals and 71% for infusions between 2010–2012 and 2016–2018.

DMT switching pattern

Patients increasingly switched from injectables to oral or infusion DMTs, while switches to injectables decreased. Follow-on DMTs after oral DMTs were predominantly oral DMT. If infusion therapy was discontinued, almost all patients continued with oral DMTs (see Figure 2).

Figure 2. Percentage of switches between injectable, oral and infusion DMTs in RRMS for time periods A) 2010–2012, B) 2013–2015, C) 2016–2018. DMT, disease-modifying therapy; RRMS, relapsing remitting multiple sclerosis.

A

B

C

Treatment effectiveness

Relapse activity

Annualized relapse rate (ARR) decreased by a mean 39% overall, 40% for injectables and 30% for orals. Infusion therapies did not decrease (Figure 3).

Figure 3: Annualized relapse rate in three time periods 2010–2012, 2013–2015, 2016–2018 on DMT overall and by application type. DMT, disease-modifying therapy.

Proportions of patients documented with 6mCDP, with progression of EDSS <3 to ≥3–5 as well as from EDSS <5 to ≥5 decreased by 39% and 23%, respectively, between the first and the last time period analyzed. In parallel, times from first symptom of RRMS to reach the defined EDSS ranges increased by 22% and 15% respectively (see Table 4).

Table 4. Six months confirmed disability progression (6m CDP. EDSS increase of ≥1.0 for patients from previous EDSS): proportion of patients reaching EDSS >=3 to 5, reaching EDSS >=5 and months from first symptom of RRMS to 6mCDP in these strata.

	EDSS <3 to ≥3–<5	**EDSS <5 to ≥5**	**Months to 6mCDP EDSS ≥3-5**		**Months to 6mCDP EDSS ≥5**	
	% patients	% patients	Mean	SD	Mean	SD
10–12	1.02	0.26	122.30	81.03	181.59	92.17
13–15	0.76	0.31	130.95	85.60	181.37	110.04
16–18	0.62	0.20	149.26	93.32	209.73	97.70
Difference from 10–12 to 16–18, %	-39	-23	+22		+15	

Maintenance of NEDA 2 and 3 criteria

There was a clear trend that patients who initated DMTs for a minimum of 3 months in these index periods remained more frequently and longer free of disease activity according to NEDA 2 (no relapse, no 6mCDP) and NEDA 3 (no relapse, no 6MCDP, no MRI progression) criteria over the three periods of time (Figure 4).

Figure 4. A. Time to failure of no-evidence-of disease-activity (NEDA) 2 (no relapse, no confirmed disability progression) and B. NEDA 3 (no relapse, no 6months confirmed disability progression, no MRI worsening) criteria in RRMS patients on DMTs after a minimum treatment period of 3 months with treatment initiation within three time periods 2010–2012, 2013–2015, 2016–2018. DMT, disease-modifying treatment; MRI, magnetic resonance imaging; RRMS, relapsing remitting multiple sclerosis.

A.

B.

Mean times to NEDA 2 and 3 failure, censored for the 3 time periods, increased continuously. NEDA 2: 10–12, 6.92 months (SD 6.66); 13 –15, 7.10 months (SD 6.55); 16–18, 7.43 months (SD 7.11). NEDA 3: 10–12, 6.70 months (SD 6.41); 13–15, 7.16 months (SD 6,42); 16–18, 7.49 months (SD 6.89).

Progression to SPMS

Between 2010 and 2018, overall 2.34% of 17,553 patients switched from RRMS to SPMS during a mean follow-up time of 5.31 years. The mean time from first symptom of MS to SPMS was 214 months (SD 113.77), almost 18 years. Time-to-SPMS progression analysis did not reveal time differences between the 3 index time periods (not shown here). There was a continuous trend towards lower numbers of patients switching to SPMS while on DMT for at least 12 months from 4.25% in 10–12, to 1.97% in 13–15, and to 1.46% in 16–18.

Discussion

The increasing number of new oral and intravenous DMTs was associated with continuously greater proportions of RRMS patients being treated between 2010 und 2018 and with earlier initiation of first therapy after diagnosis of MS had been established. Orals were increasingly preferred as first and as switching therapies, reaching 55% and about 70% of treated patients, respectively. In the years 2013 to 2015 switching of DMTs increased by 50 % including 24% of all treated patients compared to the previous period 2010 to 2012 as well as later on between 2016 to 2018 showing 14%. Lack of effectiveness was seen as an incremental driving motivation to switch, as well as adverse events and pregnancy or family planning. This raised readiness to adapt DMTs to the clinical course achieved a sustained drop of ARRs, frequency of EDSS progression and 6mCDP leading to more frequent and longer periods free of disease activity as defined by NEDA 2 and 3 criteria. Although the proportions of patients, who progressed to SPMS on therapy continuously declined as new DMTs become available, the time-to-SPMS progression of the affected patients remained unchanged at about 214 months.

Medical guidelines, regulatory processes and public discussion in Germany and other countries regarding clinical benefits, treatment strategies and drug pricing are often focused on results from the randomized controlled trials (RCTs) with an active comparator and versus placebo that led to registration of the drug[7]. However, clinical usage in a broad natural spectrum of patients and the increasing complexity of treatment options are causing a knowledge gap that RCTs are unable to fill. Thus, qualified real-world-data (RWD) are increasingly employed to evaluate optimization of therapeutic strategies[8-11]. The attempt to translate DMT efficacy studies into evidence-based clinical practice by meta-analysis of 123 unique RRMS studies provided very limited results. One main limitations was the paucity of efficacy data beyond 3 years of treatment[12]. Other initiatives addressed methodological aspects of this efficacy–effectiveness gap between results of RCTs in selected patient groups and effectiveness in real-world usage[13]. This is the first study to address population effects of a series of newly introduced DMTs in RRMS on adherence and clinical effectiveness.

Transparent data quality is the key stone of any scientific project. The physician-owned NTD MS registry can demonstrate constant data density, including a mean of 3.5 patient visits documented over the last 9 years, based on a defined minimal dataset and high data quality. This was achieved by utilization of web-based in-time data capturing and continuous development of automated and manual quality assurance measures for capturing data from 8,000 to 9,000 RRMS outpatients per year in Germany.

Definition criteria of the three time periods chosen for this study are thought to reflect periods characterized by different sets of DMTs being available for the treatment of RRMS patients. Between 2010 and 2018 the broader spectrum, in particular of oral DMTs motivated more patients to initiate DMT treatment and also to start earlier after diagnosis of RRMS. Availability of oral DMTs temporarily increased switches between

DMTs in the years after their introduction from 16% in 2010–2012 to 24% of patients on DMT in 2013–2015, with a decline back to 14% of patients switching between 2016 and 2018. This is also reflected in the time-to-discontinuation analysis, showing more frequent and quicker discontinuation of injectables in 2013–2015. Lack of effectiveness and adverse events seem to have gained in importance over time as reasons for discontinuation of DMT, mirroring increasing expectations of doctors and patients regarding benefit/risk of DMTs. Persistence on classes of DMTs after 3 years improved most noticeable for infusions moving from 50% in 2010–2012 to almost 80% in 2015–2018, injectables increasing from less than 10% to 60% and orals achieving stable persistence of about 72%. Risk rates for discontinuation decreased overall and for each application type. This suggests that over time the individual selection of efficient and well tolerated DMTs succeeds more often in all application modes of DMTs if a broader selection and better acceptance of substances is available.

Earlier initiation of treatment and more readiness to search for individual optimal therapy by switching between a greater diversity of drugs seems to have impacted treatment effectiveness. ARR decreased overall and for patients on injectables and orals approximately 30–40% between 2010–2012 and 2016–2018. However, there was no change in ARR over time for infusions. Furthermore, worsening of disability could be controlled better in parallel. The proportion of patients with EDSS reaching total sum scores >3 and > 5 decreased by 39% and 23%, respectively, and times from diagnosis to the 6mCDPs increased by 22 and 15%, respectively, when comparing time periods 2010–2012 and 2016–2018.

Comparing treatment cycles initiated in these 3 time periods, these positive developments are also reflected by continuously increasing proportions of patients maintaining NEDA 2 and NEDA 3 criteria. In addition, proportions of patients on DMT switching from RRMS to SPMS decreased each time period, but mean times to SPMS from diagnosis of RRMS remained unchanged at 17.8 years, corresponding with previous published data with a conversion time to SPMS on active treatment of 16.8 years [14]. The potential risk reduction for SPMS conversion on a broad spectrum of DMTs will have to be reevaluated in more detail as longer observation times on the new therapies become available.

The parallel improvements of reduction in ARR and disability progression, longer maintenance of NEDA 2 and 3 status in all types of DMTs, independent of their application modes, indicate that the broader selection of DMTs enable a better individual disease control in RRMS. It can be reasonably assumed that the regulatory introduced definition of high-disease-activity-labels further supported a more stringent application of the therapeutic options available. As expected, better treatment is associated with longer persistence. The observation that more efficient therapies achieved lower relapse activity in parallel with slower disability progression and longer persistence on DMTs is in line with a previous MSBase registry-based report in smaller groups of RRMS patients with advanced EDSS scores between 3 and 6[15], as well as more recent data in earlier disease stages[16]. Beside the individual patient´s fate, this is

of great socioeconomic relevance, as costs and utility in MS are highly correlated with disease severity[17] and progression inducing disease activity[18]. In contrast, continuing interferon-ß and glatiramer acetate therapy 10 years or longer without optimization of therapy in response to disease activity results in an inevitable, almost linear increase in mean EDSS[19].

This study demonstrates a clinically meaningful, population-based benefit resulting from the availability of a broader selection of DMTs over time. The introduction of oral DMTs sparked a dynamic development between 2013 and 2015 with temporarily higher proportions of DMT switches but also more readiness to initiate DMTs earlier after diagnosis of MS. The similar extent of improvement of effectiveness parameter for oral and injectable DMTs demonstrates that this population effect is based on a more effective personalized allocation in individual patients.

This study is descriptive by definition. Limitations to the study are the inclusion of only German RRMS outpatients, application of German DMT labels and regulatory specifications. The role of attrition bias due to varying follow-up times can not be ruled out, but constant mean times to discontinuation seem to reduce the risk. By including all RRMS patients giving informed consent and as distributions of clinical characteristics are balanced, indication or selection bias appear to be mitigated. Although the established data sets to characterise patients and clinical course in MS were employed the risk of residual confounding of results by unknown confounders remains. As there is no validated, generally accepted definition of SPMS, the diagnosis of SPMS is made by clinical judegment of the treating physician base don best clinical knowledge, but remains per definition retrospective.

In conclusion, these descriptive results seem to indicate that there is an overall beneficial effect for the whole MS patient population as a result of the greater selection of available DMTs, a benefit beyond the head-to-head comparative efficacy, seemingly driven by an increased probability and readiness to individualize MS therapy by doctors and patients. Nevertheless, the challenge in daily practice is the timely identification of the individually most effective DMT at a given time during the course of MS, particularly in patients with persistent disease activity on their current DMT, especially regarding the immanent risk of developing progressive disability or SPMS. Promising techniques emerge based on biomarker like neurofilament light chain[20] or B-cell activity response[21] or real-world-data-based statistical predictive algorithms[22]. As treatment decisions are driven currently by European label definitions, national cost control regulations and perceptions of physicians and patients, personalized-data-based decision support is required to further improve individual care.

Contributorship statement

SB planned the study, analysis and wrote the manuscript. FR assisted the data analysis, interpretation of results and drafting of the manuscript. HD performed the statistical

analysis and aided data interpretation. AB aided in interpreting the results and worked on the manuscript. NTD study group collected the data, performed data cleansing and data extraction from the NTD MS registry. All authors discussed the results and commented on the manuscript.

Competing interests

All authors declare that they have no competing interests.

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This project was founded by the NeuroTransdata network itself without external resources.

Data sharing statement

This project used deidentified patient data, owned by the participating doctors and provided for use in the NeuroTransData MS registry. Data can be made available upon reasonable request.

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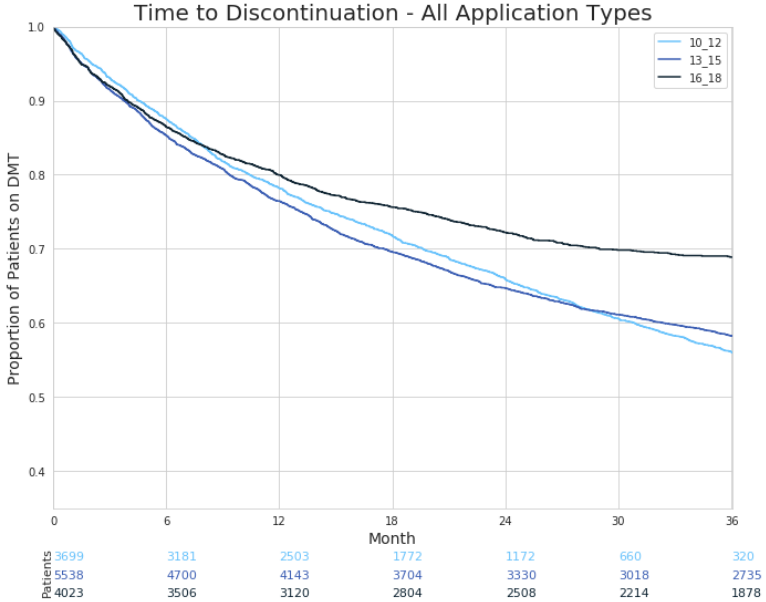
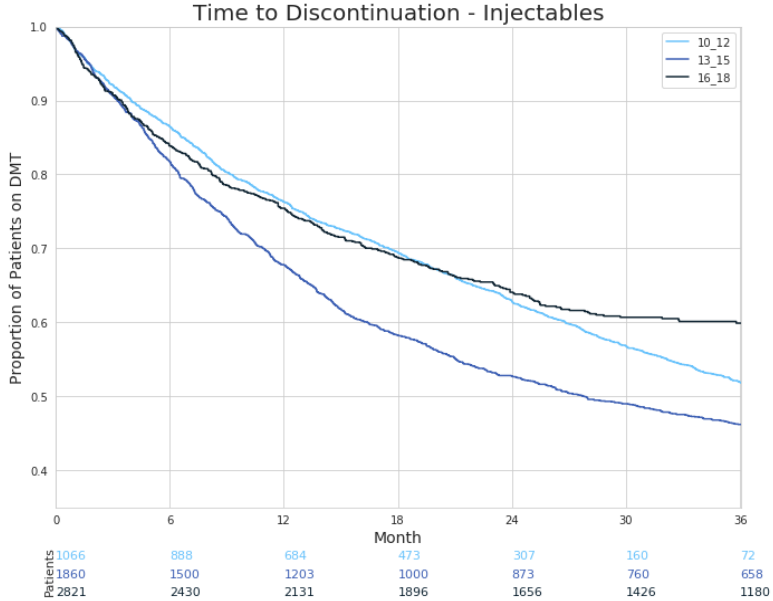
A.



B.



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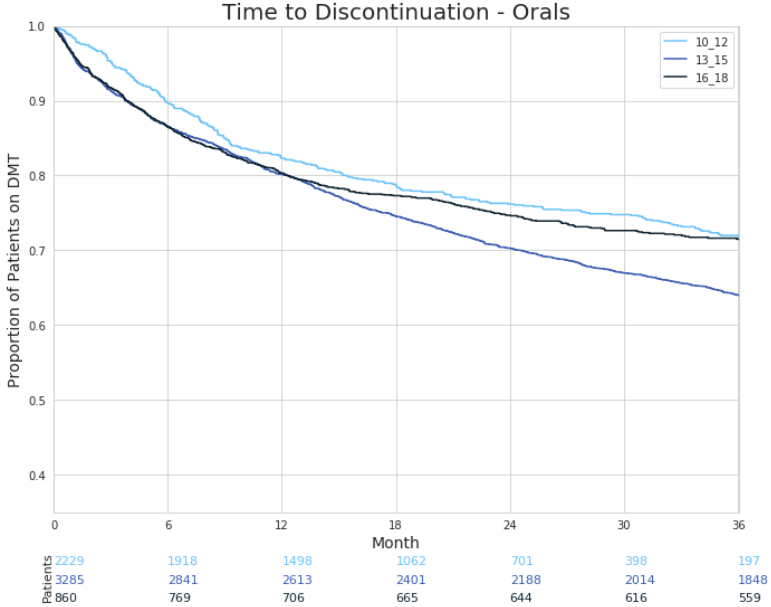
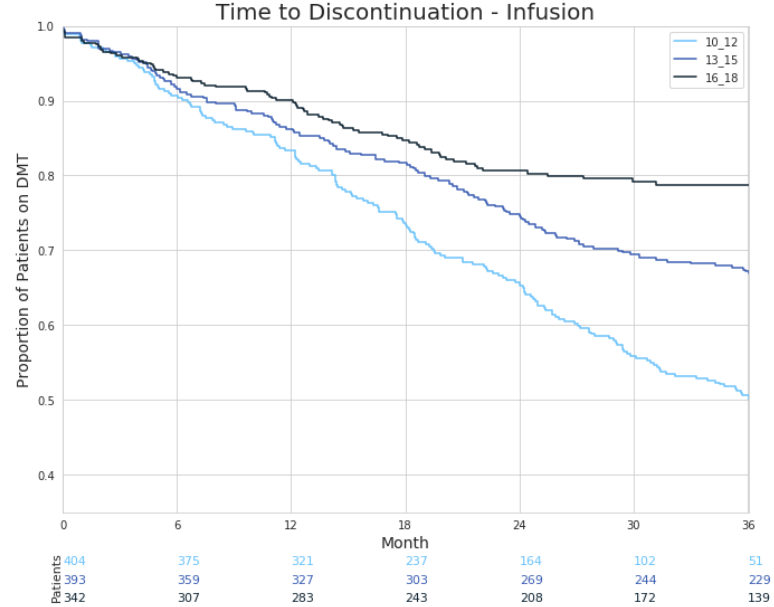
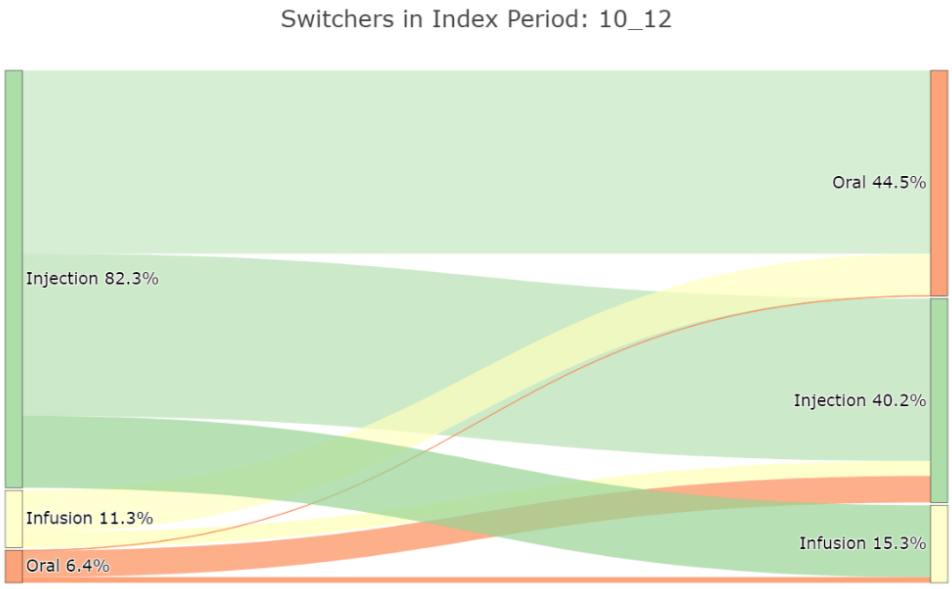
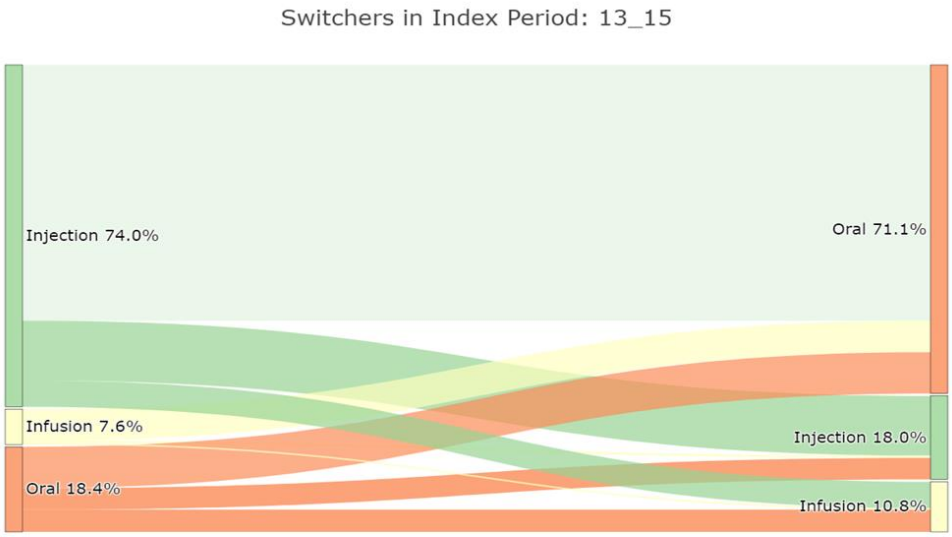
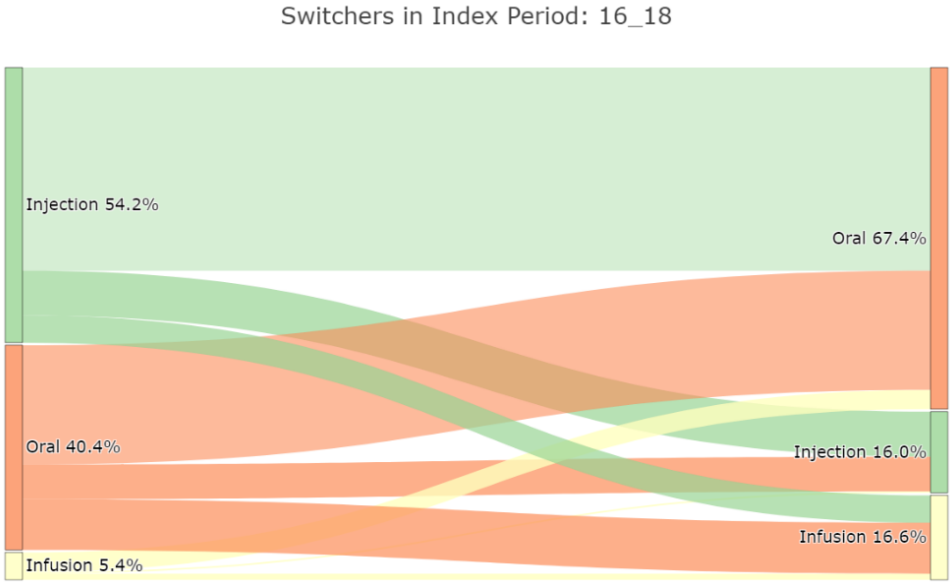


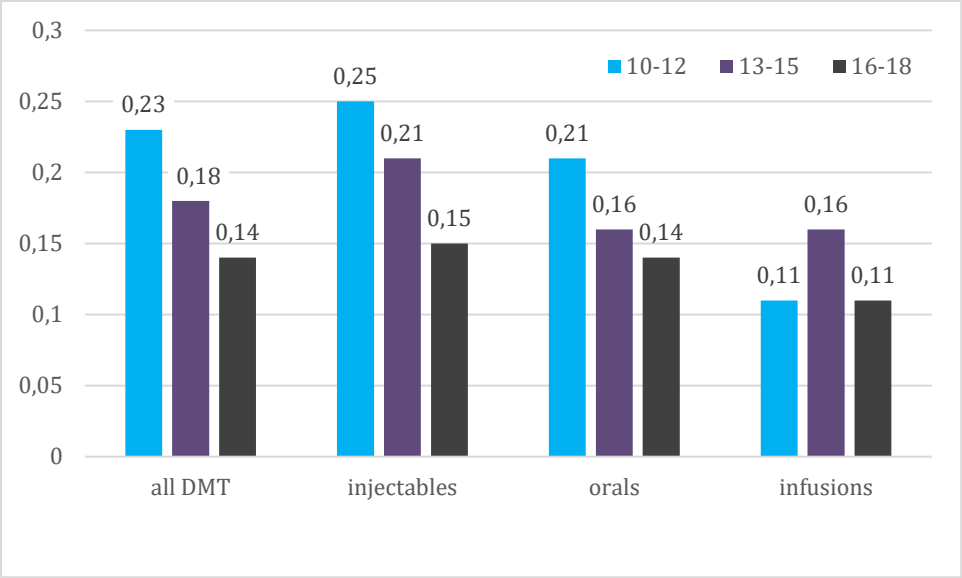
D.




Switchers in Index Period: 10_12
Injection 82.3%
Infusion 11.3%
Oral 6.4%
Oral 44.5%
Injection 40.2%
Infusion 15.3%


Switchers in Index Period: 13_15
Injection 74.0%
Infusion 7.6%
Oral 18.4%
Oral 71.1%
Injection 18.0%
Infusion 10.8%


Switchers in Index Period: 16_18
Injection 54.2%
Oral 40.4%
Infusion 5.4%
Oral 67.4%
Injection 16.0%
Infusion 16.6%



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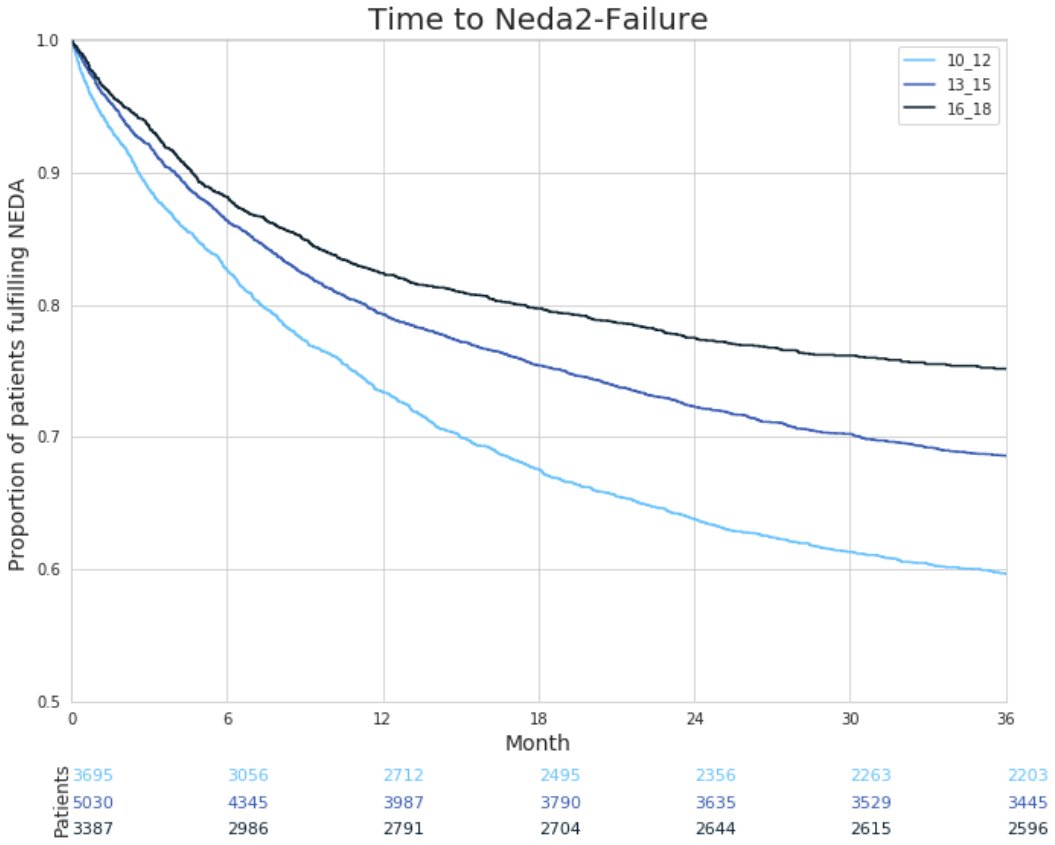
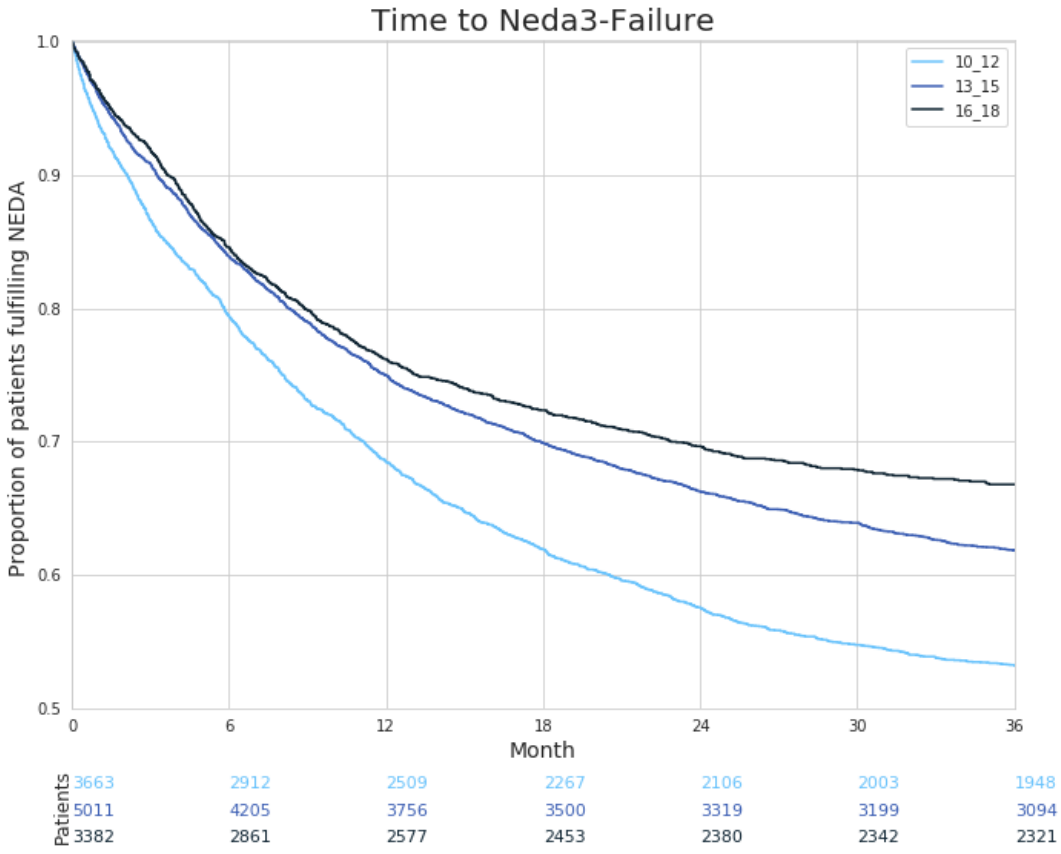

Time to Neda2-Failure
Proportion of patients fulfilling NEDA
1.0
0.9
0.8
0.7
0.6
0.5
0
6
12
18
24
30
36
Month
10_12
13_15
16_18
Patients
3695 3056 2712 2495 2356 2263 2203
5030 4345 3987 3790 3635 3529 3445
3387 2986 2791 2704 2644 2615 2596

B.


Time to Neda3-Failure
Proportion of patients fulfilling NEDA
1.0
0.9
0.8
0.7
0.6
0.5
0
6
12
18
24
30
36
Month
10_12
13_15
16_18
Patients
3663 2912 2509 2267 2106 2003 1948
5011 4205 3756 3500 3319 3199 3094
3382 2861 2577 2453 2380 2342 2321

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	☺
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	☺
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	☺
Objectives	3	State specific objectives, including any prespecified hypotheses	☺
Methods			
Study design	4	Present key elements of study design early in the paper	☺
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	☺
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	☺
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	☺
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	☺
Bias	9	Describe any efforts to address potential sources of bias	☺
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	☺
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	☺
		(*b*) Describe any methods used to examine subgroups and interactions	☺
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	☺
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	☺
		(b) Indicate number of participants with missing data for each variable of interest	☺
		(c) Summarise follow-up time (eg, average and total amount)	☺
Outcome data	15*	Report numbers of outcome events or summary measures over time	☺
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which	NA

		confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	☺
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	☺
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	☺
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	☺
Generalisability	21	Discuss the generalisability (external validity) of the study results	NA
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	☺

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.