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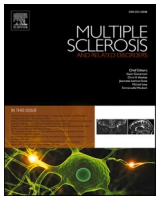

Original article

Adverse events in MS patients fulfilling or not inclusion criteria of the respective clinical trial – The problem of generalizability

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ABSTRACT

Background: The aim of this study was to evaluate how many MS patients treated with an approved DMD in routine care would have fulfilled the inclusion and exclusion criteria of phase III clinical trial and would therefore be eligible for the respective drug trial. Further, adverse events and disease progression for these patients were compared.

Methods: A comparison of patients fulfilling phase III clinical trial inclusion and exclusion criteria and those who do not with regard to sociodemographic and clinical characteristics, adverse events and disease progression. Database was the REGIMS register, a national, prospective, observational, clinical multicentre registry. 1248 MS Patients were included.

Results: 27.2% patients would have been eligible for inclusion into a phase III clinical trial of their indication. Patients who did not meet the criterion age are more likely to have a serious adverse event (SAE), whereas patients who did not fulfil the criterion relapse had a significant lower occurrence of an adverse event (AE). Non-fulfilment of other inclusion criteria (EDSS Score; medication history and MS type) did not show any significant differences in drug safety variables, AE and SAE.

Conclusion: Our results suggest that a low transferability of phase III clinical trial criteria, to patients in routine care with the exception of age, does not imply a higher risk with regard to adverse and serious adverse events.

1. Introduction

Multiple sclerosis is a chronic autoimmune disease of the central nervous system. The disease is characterised by inflammation, demyelination and axonal loss which occur in early stages. The clinical course is heterogeneous, but in most patients the initial stages are described by reversible episodes of neurological dysfunction followed by irreversible clinical and cognitive deficiencies (Filippi et al., 2018).

MS patients are treated with disease modifying drugs (DMDs) in order to prevent relapses and progression of the disease. The MS drug market is rapidly growing with several new medications approved annually thus, rapidly increasing treatment options for patients with active MS. MS is therefore an example for a dynamic market facing known challenges in pharmacovigilance. Among the latter is the question of generalizability of results of the initial phase III clinical trials to all later treated patients with the disease, which is subject of controversial discussions between clinical trialists and authorities approving new drugs since a long time. Generalizability includes the question of effectiveness of a new drug in patients who did not fulfil inclusion criteria, e.g. because of age, comorbidities or specific disease characteristics, but get treated with this drug after its approval. It also relates to the long-term safety of a new drug, especially in dynamic markets where the treatment experience for many of the newly approved drugs is limited.

Due to the high efficacy and known potential risks of biologicals in the MS therapy a long term evaluation of newly approved DMDs is of crucial importance in terms of drug safety. Phase III studies provide information on efficacy and safety for many common adverse events and thus are essential for drug approval. (Friedman et al., 2010) Nevertheless, phase III studies cannot reliably detect rare adverse events. Furthermore, drug safety analysed in phase III clinical trials with strict in- and exclusion criteria might not adequately represent the safety profile in the widespread clinical use after drug approval. Considering the setting of phase III clinical trials the transfer of results into clinical routine might be restricted causing a lack of generalizability. (Fischer et al., 2012; He et al., 2020) Therefore, post marketing studies such as

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phase IV studies, post admission surveillance studies and registries are essential for a holistic drug life cycle insuring additional information in terms of safety and efficacy.

Natalizumab was the first monoclonal antibody that was approved in 2006 for MS therapy by the European Commission. (European Medicines Agency) Another landmark in DMD development was, fingolimod (2011), the first oral MS medication. Alemtuzumab (2013) and ocrelizumab (2018) are further monoclonal antibodies which have been approved for MS, with ocrelizumab having an approval for the treatment of both PPMS and the more common RRMS phenotype. (Tintore et al., 2019) Recently approved (2020) MS DMDs are ozanimod and siponimod. (Jalkh et al., 2020) Considering the risk of severe adverse events (SAE) in patients using DMDs, drug monitoring is a central component of response and safety. (Simbrich et al., 2019) Daclizumab is a MS DMD that was withdrawn from the market in 2018, after reports of autoimmune encephalitis in Europe. (European medicines agency - CHMP; BIOGEN and ABBVIE, 2018) Cladribine has been associated with thrombocytopenia, leukopenia, and anaemia possibly as a result of higher doses administration. (Beutler et al., 1994) Fingolimod and natalizumab have been associated with progressive multifocal leukoencephalopathy (PML). (Berger et al., 2018; Bloomgren et al., 2012) MS registries that have been implemented in several countries play an important role in drug monitoring and the implementation of drug safety through long-term assessment of the frequency of potential rare side effects. (Flachenecker and Stuke, 2008; Willis et al., 2012)

The aim of our study was to evaluate how many MS patients treated with an approved DMD in routine clinical care would have fulfilled inclusion and exclusion criteria of phase III clinical trial and would therefore been eligible for the respective drug trial. A further goal was to compare patients fulfilling inclusion and exclusion criteria and those who do not with regard to sociodemographic and clinical characteristics, adverse events and disease progression.

2. Methods

2.1. Ethics

The study was approved by the local Ethics Committee of the Medical Chamber Westphalia-Lippe and the School of Medicine University of Muenster, Germany (Approval number: 2013–308-b-S). Further, the study was approved by the Ethics Commission of the School of Medicine University of Bochum (Approval number: 4588–13). All patients gave written informed consent.

2.2. Data source and study population

REGIMS is a German immunotherapy registry and part of the disease-orientated Competence Network Multiple Sclerosis (Krankheitsbezogenes Kompetenznetz Multiple Sklerose [KKNMS]). REGIMS primary goal is to record the frequency, type, characteristics and effects of adverse events in current and new immunotherapeutic DMDs used in routine clinical care of MS patients. REGIMS is a national, prospective, observational (i.e., non-interventional), clinical multicentre registry. Further REGIMS details have been described elsewhere. (Simbrich et al., 2021)

Included in this analysis were patients enroled in REGIMS between Oct. 2013 and Sept. 2020 who started treatment with one of the following DMDs: ocrelizumab, cladribine, daclizumab, dimethyl fumarate, teriflunomide, alemtuzumab, fingolimod, natalizumab, mitoxantrone, glatiramer acetate, peginterferon β−1a, interferon β−1a and interferon β−1b. 1748 REGIMS patients receiving a DMD were initially included, but analysis was restricted to the 1660 patients who had a relapsing MS type, due to the small number of patients with PPMS. Patients with incomplete data on DMD start, EDSS (Expanded Disability Status Scale) score, clinical course, relapse data and implausible medication history data were additionally excluded, leaving 1493 baseline patients. 1248 patients with a baseline and follow up visits were used for the analysis (Supplement Table S1).

2.3. Data analysis

Post approval compliance with selected phase III clinical trial criteria was based on the 'Summary of Product Characteristics' for each DMD, published by the European Medicines Agency and the respective phase III clinical trial providing information on efficacy and safety. A complete summary of inclusion and exclusion criteria applied in this study were published elsewhere. (Jalusic et al., 2021) Mostly, patients were included if they were between 18 and 55 years old; had a RRMS clinical course with at least 2 relapses within the last 2 years prior to randomization or 1 relapse in the year before and/or a MRI scan of the brain showing abnormalities consistent with multiple sclerosis (e. g. at least one gadolinium-enhancing lesion 0 to 6 weeks to randomization). Given that the exact number of T2 lesions is not collected in REGIMS, magnetic resonance imaging (MRI) was not taken into consideration. A further selection criterion was an EDSS Score between 0.0 und 5.0 (Supplement Table S2). Medication history was a common exclusion criterion in clinical trials (Supplement Table S3). The assessment of in- and exclusion criteria was done for patients with complete baseline data and follow up visits. In the first step the proportion of patients eligible to clinical trials across different DMDs was analysed. In the next step the percentage of patients fulfilling each criterion of the phase III clinical trial was described for every DMD separately. Finally, patients who did not meet all in- and exclusion criteria for a certain drug were compared with those who did in term of clinical and sociodemographic characteristics.

Outcome assessment was based on patient's last follow up visit. Analysed was a follow-up period of up to 30 months after baseline. For the outcome analysis the following items were used: adverse event (AE), serious adverse event (SAE), relapse /disease progression, DMD change, EDSS. Documentation was done in an Electronic Data Capture (EADC) system by physicians in the study centres. Safety data (AE) in REGIMS are reported irrespective of causality. SAEs are instantly delivered to the registry and reported to the holder of marketing authorisation. Relapses are not documented as AEs. Change in EDSS score was defined as a difference between the baseline and follow up EDSS score of at least 0.5 points.

For categorical, between group comparisons of eligible and ineligible patients the chi-square tests were used and for continuous variables Students *t*-test. In order to investigate the difference in drug safety data (AE and SAE) between patient's who did not and those who fulfilled all five predefined in- and exclusion criteria, logistic regression models were applied. A p-value of <0.05 was considered statistically significant. Analyses were performed using STATA/SE 13.0.

3. Results

3.1. Demographic and clinical characteristics

In total 1248 patents with at least one follow-up visit were analysed in this study. Mean time to follow up was 6.7 months (standard deviation [SD] = 3.1). Supplement Table S1 describes the flowchart of inclusions into the analysis. Demographic and clinical characteristics are summarised in Table 1. The majority of the patients were females (70.1%), mean age was 37.6 (SD = 11.1) with a range from 16 to 75 years. The mean number of relapses 24 months within baseline was 1.5 (SD: 1.6). 5.2% of the REGIMS patients had a relapse at baseline. Mean EDSS Score at baseline was 2.7 (SD: 1.7). 94.6% of patients suffered from RRMS, 4.3% from SPMS and 1.0% had a CIS. In total 1356 (S)AE were recorded. Cold (6.13%), influenza like illness (2.95%), lymphopenia (2.80%) and urinary infection (2.07) were the most often observed (S) AEs (Supplement Table S4).

Table 1
Demographic and clinical characteristics of the Regims patients.

Characteristics	Baseline and follow up (Outcome analysis)		
	Total	Fulfilling all criteria	Not fulfilling all criteria
Patients (N).	1248	340	908
Female,%	70.1	68.8	70.6
Age, years, mean (SD)	37.6 (11.1)	34.0 (8.9)	38.9 (11.6)
Age 1st symptom's, mean (SD)	29.5 (10.1)	27.8 (8.5)	30.1 (10.6)
Age diagnosis, years, mean (SD)	31.5 (10.5)	29.5 (8.9)	32.2 (10.9)
Disease duration, mean (SD)	9.7 (7.8)	7.1 (6.6)	10.7 (8.0)
EDSS-Score, mean (SD)	2.7 (1.7)	2.3 (1.2)	2.8 (1.8)
Relapses[a], mean (SD)	1.5 (1.6)	2.8 (1.7)	1.0 (1.3)
Relapse baseline[b],% (patients)	5.2	8.6	3.9
RRMS,%	94.6	99.4	92.8

DMT: disease-modifying therapy; EDSS: expanded disability status scale; RRMS: relapsing-remitting multiple sclerosis
[a] Nummber of relapses 24 months within randomization
[b] Relapse at baseline.

3.1.1. Post approval compliance with selected phase III clinical trial criteria

Across all analysed drugs, 27.2% of the patients would have been eligible for inclusion into a phase III clinical trial if all five predefined criteria were applied. 61.5% would have been included into the respective clinical trial if the selection criterion "relapse" was dropped.

Hence, the highest exclusion proportion (58.5%) was due to non-fulfilment of the selection criterion "relapse", followed by "medication history" (26.4%). 9.8% of the patients did not fulfil the criterion "EDSS score", while 8.9% did not comply with the criterion "age". Finally, "clinical course" led to the lowest exclusion percentage (3.5%).

Table 2 shows the percentages of REGIMS patients who would have been included in a phase III clinical trial of the respective drug. Patients treated with alemtuzumab (53.0%) and interferons (53.9%) showed the highest concordance with clinical trial criteria, fulfilling all five selection criteria. Patients treated with mitoxantrone (10.0%) and teriflunomide (12.1%) showed the lowest concordance. 35.1% of fingolimod and 25.4% of glatiramer acetate patients would have been selected for the respective phase III clinical trial fulfilling all four admission criteria (age, EDSS score, relapse, clinical course).

The highest concordance with all admission criteria, when dropping the criterion "relapse", was attained in patients treated with fingolimod (86.9%) and alemtuzumab (81.6%). In contrast, the lowest was observed in those treated with mitoxantrone (10.0%), natalizumab (46.0%), teriflunomide (48.3%), and dimethyl fumarate (49.1%).

3.1.2. Comparison of patients treated with DMDs post approval

Table 3 shows the comparison of MS patients fulfilling all predefined phase III trial inclusion criteria and those who did not. The latter group was older at therapy start, as well as at the time of diagnosis and at age of first symptoms with the exception of those treated with alemtuzumab, cladribine and interferons. Patient who did not fulfil all criteria had a higher EDSS Score and less relapses in the two years before treatment start.

3.1.3. Outcome comparison within regims patients

amongst all REGIMS patients, 40.9% had at least one AE and 8.4% at least one SAE. 32.7% had a disease progression or relapse during the mean follow up time of 6.7 months. Table 4 shows the outcome comparison between patients fulfilling all five predefined inclusion criteria and patients missing at least one criterion (a), as well as the comparison when the criterion "relapse" is omitted (b).

Across all DMDs, the percentage of patients having at least one adverse event was higher in the group who fulfilled, compared to the one who did not fulfil all inclusion criteria (47.8 % vs. 38.3%). When comparing the groups for single drugs, this result was also observed in patients treated with alemtuzumab, fingolimod and natalizumab. In contrast, for patients treatedwith ocrelizumab and dimethyl fumarate those not fulfilling all inclusion criteria had slightly more AEs.

For SAE across all DMDs 8.7% of patients who fulfilled all five inclusion criteria experienced at least one SAE, compared to 8.3% of those who did not. Patients treated with alemtuzumab had also no difference in SAEs based on the fulfilment of admission criteria. In contrast to that, the proportion of patients who had at last one serious event and received ocrelizumab or dimethyl fumarate was higher in the non-fulfilment group. After dropping the criterion "relapse", in the group of patients not fulfilling predefined four criteria 9.3% experienced at least one serious event, while in the other group it was 7.9%.

In order to investigate a relationship between drug safety variables (AE; SAE) and the fulfilment (yes-no) of predefined inclusion criteria (criterion age, criterion EDSS Score, criterion medication history, criterion relapses, criterion MS Type) a logistic regression analysis was conducted. Table 5a shows the results of the logistic regression analysis where the dependant variable is AE. Yes equals 1 if a patient had at least one AE and 0 otherwise. The results of the multiple binary logistic regression indicate that, patients fulfilling the criterion relapses have higher odds of having AEs than patients not fulfilling this criterion (OR: 1.39; 95% CI: 1.10 – 1.75; $p = 0.005$). Table 5b shows the results of the logistic regression analysis where the dependant variable is SAE. Patients fulfilling the criterion age have lower odds of having a SAE then patients not fulfilling this criterion (OR: 0.50; 95% CI: 0.28 – 0.91; $p = 0.02$).

A further logistic regression analysis (Table S5a and S5b) evaluated the relationship between AE/SAE and individual patient's

Table 2
Percentage of Regims patients fulfilling phase III clinical trial selection criteria. $N = 1248$.

DMT	Patients (N)	% of patients fulfilling each criterion					% patients fulfilling all criteria	% patients fulfilling 4 criteria[a]
		Age	EDSS Score	Relapse	Clinical course	Medication history		
All drugs	1248	91.1	90.2	41.5	96.6	73.6	27.2	61.5
Ocrelizumab	89	89.9	78.7	34.8	88.8	68.5	22.5	53.9
Cladribine	14	100.0	85.7	35.7	100.0	71.4	21.4	64.3
Daclizumab	10	100.0	90.0	70.0	100.0	50.0	40.0	50.0
Dimethyl fumarate	108	90.7	92.6	30.6	99.1	57.4	16.7	49.1
Teriflunomide	58	81.0	89.7	20.7	100.0	65.5	12.1	48.3
Alemtuzumab	168	98.8	92.3	64.3	98.2	89.9	53.0	81.6
Fingolimod	214	93.5	93.0	40.2	96.3	n/a	35.1	86.9
Natalizumab	422	89.1	89.3	34.6	99.1	56.9	14.9	46.0
Mitoxantrone	20	60.0	75.0	95.0	100.0	25.0	10.0	10.0
Glatiramer acetate	67	86.6	92.5	28.4	85.1	n/a	25.4	73.1
Interferons	78	97.4	96.2	66.7	91.0	84.6	53.9	73.1

[a] Percentage of patients fulfilling all criteria when selection criterion relapse was excluded.

Table 3
Mean difference (Δ) between patients fulfilling all inclusion criteria for phase III clinical trials (Jalusic et al., 2021) compared to patients who would not.

Mean Δ	Ocrelizumab	Cladribine	Daclizumab	Dimethyl- fumarate	Teriflunomide	Alemtuzu-mab	Fingolimod	Natalizumab	Mitoxantrone	Glatiramer acetate	Interferons
Patients[a]	69	11	6	90	51	79	139	359	18	50	36
Age (years)	+9.6 ***	−4.1	+4.3	+4.8	+8.1*	+2.7	+4.9**	+4.9***	+9.6	+5.3	+4.2
Age diagnosis (years)	+3.9	−13.1	+3.7	+2.6	+4.9	+0.5	+3.2*	+3.5**	+8.7	+5.1	−0.1
Age symptoms (years)	+3.0	−15.7*	+2.6	+1.5	+0.8	0.03	+3.7*	+3.0*	+20.6*	+4.0	−0.3
EDSS-Score	+1.3*	1.0	2.1	−0.3	+0.9	+0.4	+0.3	+0.5*	+0.6	+0.6	+0.7 *
Relapses 24 months, No	−1.7***	−1.6*	−1.4 *	−1.8***	−1.4***	−2.1***	−2.1***	−1.6***	+0.1	−1.5***	−0.8*

[a] Number of patients missed at least one selection criterion; DMT: disease-modifying therapy; EDSS: expanded disability status scale; No: number., *$p<.05$; **$p<.01$; ***$p<.001$.

characteristics (age, EDSS Score, number of relapses, MS type, number of previous DMDs, disease duration). This analysis shows that patients with more relapses have higher odds of having AEs (OR: 1.15; 95% CI: 1.06 - 1.25; p = 0.01).

When comparing the item relapse/disease progression, the percentage of patients who had a relapse or disease progression was slightly higher in the group of patients fulfilling all inclusion criteria (34.4% vs 32.1%). Alemtuzumab, dimethyl fumarate and fingolimod patients showed the same pattern in both groups, while for patients treated with ocrelizumab and natalizumab the progression was higher in the not concordant group.

The proportion with treatment change of a DMD was slightly higher in the group of patients who did not fulfil all predefined criteria (3.2 % vs 2.7%). An exception from this pattern were patients receiving natalizumab with 3.2% of them changing the DMD while fulfilling all criteria compared to 2.0% in those who did not.

Across all DMDs patients fulfilling all predefined inclusion criteria (35.5%) had a stronger EDSS decrease during the follow up than patients not fulfilling all criteria (28.1%).

4. Discussion

In this study we analysed the effects of transferring phase III clinical trials inclusion and exclusion criteria to MS patients treated with DMDs in clinical routine by investigating differences in drug safety (AE; SAE) and clinical characteristics between the two groups. We found that the majority of patients treated with an approved MS DMD in routine clinical care would not have met all predefined inclusion criteria of the respective phase III clinical trial. Main reason for this result was the criterion “relapse”. When this criterion is dropped, the proportion of patients fulfilling the other criteria increased to 61.5% on average. This result is in concordance with our previous published study based on the German MS Register (GMSR) (Jalusic et al., 2021) and with similar studies addressing generalizability of clinical trials in other diseases. (He et al., 2020) Despite the large proportion of patients who would not have been recruited into the respective clinical trial, the criteria “age” and “relapse” were the only predictor variables with a statistical significant relation to drug safety outcomes. Since no generalizability studies of clinical trials for DMDs analysing safety data in MS patients have been published yet, this result cannot be compared to other studies.

We also found that the probability of an AE in patients fulfilling the criterion relapse is higher than in patients not fulfilling this criterion. The reduction of the annualized relapse rate is a frequent endpoint in clinical trials and serves as a proxy for disease activity. Phase III clinical trials include patients with at least one relapse during one year or at least two relapses in two years prior to randomisation. The criterion “relapse” was the criterion with the highest percentage of non-fulfilment. In this study, we analysed treatment-naive patients and patients with a treatment history of MS DMDs. Receiving a high-efficacy DMD in the period preceding baseline might account for some patients having a lower relapse rate. Since a low rate of relapses indicates low disease activity, the non-fulfilment of this criterion may just show a successful treatment and is not considered as a potential safety risk in the drug therapy.

Next to the criterion “relapse” patients showed the lowest concordance with the criterion “medication history”. Washout periods as required in most phase III clinical trials are hardly achievable in routine clinical care. In case patients do not respond to current treatment or have at least one relapse, guidelines recommend to switch to a second line therapy. (Montalban et al., 2018) Additionally, Sepulveda et al. showed that discontinuing a treatment with fingolimod without a suitable DMD switch resulted in rebound relapses. (Sepúlveda et al., 2020) This risk was also observed if natalizumab treatment is stopped without an appropriate DMD switch. (Mustonen et al., 2020) Subsequently a medication history without DMD is nowadays rare and most patients are treated with multiple DMDs over their disease course. Our analysis showed that missing the criterion medication history does not imply a

Table 4
Outcome comparison between patient groups.

a) all five predefined inclusion criteria and patients missing at least one criterion												
Disease modifying drug (DMD)		All DMDs		Ocrelizumab		Dimethyl fumarate		Alemtuzumab		Fingolimod		Natalizumab	
Fullfilment of all 5 inclusion criteria		Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Adverse event (AE) [%]		47.8	38.3	15.0	20.6	23.5	32.6	62.1	56.6	59.5	49.3	43.6	35.2
Serious adverse event (SAE) [%]		8.7	8.3	0	2.9	0	8.1	12.6	13.2	14.9	11.8	8.1	7.5
Relapse /disease progression [%]		34.4	32.1	35.0	36.2	33.3	31.1	37.1	34.2	41.3	28.8	27.0	33.4
Change in DMD [%]		2.7	3.2	0	7.3	0	4.5	0	1.3	2.7	2.9	3.2	2.0
EDSS [%]	No change	31.5	38.6	47.4	60.0	25.0	53.4	21.6	35.0	33.8	34.4	30.0	34.2
	Increase	33.0	33.4	15.8	21.5	31.3	22.7	31.8	32.5	33.8	32.8	31.7	37.7
	Decrease	35.5	28.1	36.8	18.5	43.8	23.9	46.6	32.5	32.4	32.8	38.3	28.1
b) four predefined inclusion criteria (without relapse) and patients missing at least one of those													
Disease modifying drug (DMD)		All DMDs		Ocrelizumab		Dimethyl fumarate		Alemtuzumab		Fingolimod		Natalizumab	
Fullfilment of 4 inclusion criteria		Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Adverse event (AE) [%]		43.0	37.5	12.5	27.5	30.6	31.5	41.8	65.5	54.1	44.4	34.4	38.2
Serious adverse event (SAE) [%]		7.9	9.3	0.0	5.0	2.0	11.1	11.9	17.2	12	18.5	6.8	8.3
Relapse /disease progression [%]		33.3	31.7	35.4	36.6	34.0	29.1	36.5	32.3	33.3	32.1	32.0	32.9
Change in DMD [%]		2.7	3.6	4.2	7.3	3.9	3.6	0.7	0.0	2.2	7.4	1.6	2.6
EDSS	No change [%]	36.0	37.6	53.3	61.5	44.0	53.7	27.4	30.0	33.5	38.5	35.7	31.8
	Increase [%]	32.0	35.4	22.2	18.0	24.0	24.1	31.1	36.7	34.1	26.9	31.9	40.9
	Decrease [%]	32.0	27.0	24.4	20.5	32.0	22.2	41.5	33.3	32.4	34.6	32.4	27.3

Table 5a
Odds ratios for the risk of adverse events according to fulfilment of clinical trial inclusion criteria.

AE	Univariate			Multivariate		
Inclusion criteria	OR	95% CI	P-Value	OR	95% CI	P-Value
Age	0.982	0.659 – 1.464	0.929	0.939	0.623 – 1.416	0.766
EDSS Score	0.965	0.658 – 1.414	0.854	0.860	0.576 – 1.285	0.463
Medication history	1.276	0.982 – 1.657	0.068	1.287	0.987 – 1.678	0.0.63
Relapses	1.402	1.113 – 1.767	0.004	1.391	1.103 – 1.754	0.005
ms type	1.699	0.859 – 3.363	0.128	1.848	0.918 – 3.721	0.085

dependant variable is adverse event [AE] (1= at least one serious AE; 0 = no AE). Univariate adjusted to the inclusion of a single criterion as independent variable. Multivariate adjusted to the inclusion of all other listed criteria simultaneously.

Table 5b
Odds ratios for the risk of serious adverse events according to fulfilment of clinical trial inclusion criteria.

SAE	Univariate			Multivariate		
Inclusion criteria	OR	95% CI	P-Value	OR	95% CI	P-Value
Age	0.492	0.277 – 0.874	0.016	0.503	0.278 – 0.910	0.023
EDSS Score	0.607	0.339 – 1.088	0.093	0.599	0.324 – 1.107	0.102
Medication history	1.284	0.793 – 2.080	0.309	1.404	0.859 – 2.296	0.175
Relapses	1.101	0.733 – 1.654	0.643	1.101	0.731 – 1.658	0.646
ms type	1.821	0.434 – 7.656	0.413	2.580	0.595 – 11.177	0.205

dependant variable is adverse event [SAE] (1= at least one serious SAE; 0 = no SAE). Univariate adjusted to the inclusion of a single criterion as independent variable. Multivariate adjusted to the inclusion of all other listed criteria simultaneously.

higher risk in terms of drug safety.

DMDs for MS Patients in Germany are prescribed by physicians of various specialization. The German Society of Neurology published a Guideline for Diagnosis and therapy of MS, neuromyelitis optica spectrum diseases and MOG-IgG-associated diseases with recommendations for DMD prescriptions in MS patients. (Hemmer et al., 2021) Supplement Figure S1 shows the therapy algorithm for initial setting/escalation according to the current guideline. However, it is unknown how many physicians follow this guideline.

Elderly patients are often excluded from phase III clinical trials and additional information on safety of DMDs in ageing population is required. We showed that across all drugs 91.1% of the patients fulfilled the criterion age. The results of the logistic regression indicate that patients not fulfilling the predefined criterion age have a higher risk of having a SAE. The probability of different comorbidities and therefore the interaction of comorbidities and DMDs in elderly MS patients is higher than in younger patients. (Capkun et al., 2015) This presents a potential risk in the drug therapy of older MS patients.

Our study has several limitations. For some DMDs the number of patients was small, because of exclusion of patients with incomplete documentation or because of a low drug market share in general. Due to incomplete MRI data this criterion was not applied to the REGIMS patients, although some of the phase III clinical trials applied magnetic resonance imaging (MRI) of the brain indicating MS comparable abnormalities as an inclusion criterion. Since the exact dates on relapse timing are unknown, no statement can be made whether a AE is relapse related or not.

The results of our study suggest that a low transferability of single phase III clinical trial criteria (EDSS, medication history, relapse) to patients in routine clinical care does not imply a higher risk in terms of drug safety. Elder patients, who are frequently excluded from clinical trials, however have a higher risk of having a serious adverse event. Generalizability of clinical trial results refers to the question if the tested drug would have the same effect and the same adverse event profile in patients who were excluded from the trial. But the answer to this question usually does not differentiate between patient's characteristics that are important in this context (e.g. pregnancy, specific comorbidies or disease cause) or less important (e.g. age) in the judgement of generalizability of results. Thus, assuming an adverse event risk as in the trial for a patient who is 5 years older than the inclusion criterion is probably more valid than assuming the same effect for a pregnant woman in the second trimester of pregnancy. However, the performance of a drug should also be verified, when used outside clinical trials, e.g. in registry based results or other study designs. Thus clinical routine data from prospective cohort studies and registers, such as REGIMS are needed to identify the risks and benefits of DMDs in different groups of patients.

Credit author statement

K.O.J., D.E., A.S. and K.B. conceptualized the study. K.O.J. and K.B. designed the study, analysed and interpreted the data. K.O.J. wrote the original draft. D.E. and A.S. reviewed the manuscript for intellectual content. All authors critically reviewed and approved the final version of the manuscript.

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Supplementary materials

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