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ORIGINAL ARTICLE

Quantifying the risk of disease reactivation after interferon and glatiramer acetate discontinuation in multiple sclerosis: The VIAADISC score

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Abstract

Background and purpose: There is a lack of evidence guiding discontinuation of disease-modifying therapy (DMT) in relapsing multiple sclerosis (RMS). Thus, the objective of this study was to generate and validate a risk score for disease reactivation after DMT discontinuation in RMS.

Methods: We drew a generation and validation dataset from two separate prospectively collected observational databases including RMS patients who received interferon-β or glatiramer acetate for ≥12 months, then discontinued DMT for ≥6 months and had ≥2 years of follow-up available. In the generation sample (n = 168), regression analysis was performed to identify clinical or magnetic resonance imaging (MRI) variables independently predicting disease reactivation after DMT discontinuation. A predictive score was calculated using the variables included in the multivariable model and applied to the validation sample (n = 98).

Results: The variables included in the final model as independent predictors of disease reactivation were age at discontinuation, MRI activity at discontinuation, and duration of clinical stability (all $p < 0.001$). The resulting score was able to robustly identify patients at high (83%–85%), moderate (36%–38%), and low risk (7%) of disease reactivation within 5 years after DMT discontinuation in both cohorts.

Conclusions: The composite VIAADISC score is a valuable tool to inform and support patients and neurologists in the process of decision making to discontinue injectable DMTs.

KEYWORDS
discontinuation, disease-modifying therapy, multiple sclerosis, reactivation, risk AUTHOR: Please check the list of abbreviations.

Abbreviations: CI, confidence interval; DMT, disease-modifying therapies; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; MRI, magnetic resonance imaging; MS, multiple sclerosis; RMS, relapsing multiple sclerosis; SE, standard error; SPMS, secondary progressive multiple sclerosis; VMSD, Vienna Multiple Sclerosis Database.

INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune-mediated inflammatory neurological disease carrying the risk of physical and cognitive disability [1]. Over the last quarter century, an ever-increasing number of immunomodulating or immunosuppressive disease-modifying therapies (DMTs) have proven to effectively reduce the number of relapses, brain magnetic resonance imaging (MRI) activity, and to a lesser extent disability progression in relapsing MS (RMS) [2]. Consequently, MS treatment has changed dramatically toward applying treatment early and striving to suppress disease activity below the level of detectability [3].

However, inflammatory activity declines over the natural course of MS and prolonged periods of stability may prompt patients and neurologists to consider DMT discontinuation, especially in cases of persistent side effects, increasing DMT-associated risks, or declining adherence (e.g., syringe fatigue) [4]. Although this is a situation commonly occurring in clinical practice, there is a lack of evidence guiding treatment decisions regarding DMT discontinuation.

Although premature discontinuation may lead to recurring disease activity and accumulating disability, some studies have recently indicated that patients with older age, a low degree of disability, and extended periods without clinical or MRI evidence of disease activity display low probability of disease reactivation after DMT discontinuation [5–8].

Hence, the degree of risk associated with DMT discontinuation depends on individual factors, and the type of DMT used needs to be taken into account when counseling MS patients.

The objective of this study was to generate and validate a clinical and MRI-based composite score able to identify individual RMS patients with a high risk of experiencing disease reactivation after discontinuation of an injectable DMT.

METHODS

Patients and definitions

This study was performed using two separate prospectively collected datasets: a generation dataset consisting of a previously published cohort out of the Innsbruck Multiple Sclerosis Database and an independent validation dataset [9].

The generation dataset is derived from a previously published study on RMS patients who received an injectable DMT for a minimum of 12 months, then discontinued DMT for at least 6 months and had 2 or more years of follow-up available without documented pregnancy during the follow-up period [8]. In addition, inclusion criteria required a cerebral MRI performed within 6 months prior to discontinuation of DMT (MRI at discontinuation) and another cerebral MRI performed within 24 months prior to the MRI at discontinuation (MRI before discontinuation).

The validation dataset was drawn from the Vienna MS Database (VMSD) using the same inclusion criteria. The VMSD is established at the MS Clinic of the Department of Neurology, Medical University of Vienna, which serves as both primary and reference center mainly for Vienna and its geographical catchment area. By February 2020, a cohort of 1121 MS patients diagnosed according to respective McDonald criteria had been included [10–12]. VMSD case reports include demographic data, details of MS course (disease onset, time to diagnosis, relapses, Expanded Disability Status Scale [EDSS], and onset of secondary progression), diagnostic investigations (MRI, cerebrospinal fluid findings), and DMT history (including initiation, interruption, changes, and adverse effects). Data are collected retrospectively at first visit and prospectively whenever the patient returns for scheduled (every 3–6 months) follow-up or unscheduled visits.

Reasons for discontinuation were divided into three categories: (i) adverse events, (ii) patient's decision (including desire of pregnancy), and (iii) stable disease course (subjectively defined by the treating neurologist and/or patient). A relapse was defined as patient-reported symptoms objectified by a neurologist or objectively observed signs typical of an acute central nervous system inflammatory demyelinating event, current or prior to the visit, with a duration of at least 24 h in the absence of fever or infection, separated from the last relapse by at least 30 days [11]. EDSS worsening was defined as a confirmed EDSS increase of ≥1.0 point in patients with a baseline score of ≤5.5, or an increase of ≥0.5 points in patients with a baseline score of >5.5 sustained for at least 12 months as compared to baseline [13].

Duration of clinical stability was defined as the number of years since the last documented relapse and/or EDSS worsening before DMT discontinuation.

Disease reactivation was defined as a combined end point including occurrence of relapse and/or EDSS worsening and/or restart of DMT.

MRI parameters obtained were T2 lesion load, increase in T2 lesion load, and presence of gadolinium-enhancing (Gd+) lesions. Increase in T2 lesion load was defined as three or more either new or size-enlarged T2 lesions in MRI at discontinuation compared to MRI before discontinuation [14]. MRI activity was defined as increase in T2 lesion load and/or presence of Gd+ lesions in MRI at discontinuation.

Statistical analysis

The scoring system was developed and validated through the following steps:

1. In the generation dataset, univariate Cox regressions were performed to identify those variables significantly associated with the time to disease reactivation. Receiver operating characteristic analyses were used to define optimal possible cutoff values of continuous variables for prediction of disease reactivation. Those variables with a p value <0.2 entered a multivariable Cox regression where the time to disease reactivation was the dependent variable. A p value of 0.01 was used to select the variables to be retained in the final model. Based on the

regression coefficients provided from this model, all retained variables were allocated integral values expressing the relatively weighted impact of each variable with the overall predictive score being the sum of these values.

2. The predictive power of this score was tested by Cox regression in the generation dataset with time to disease reactivation as the dependent variable and the predictive score as the independent variable. Kaplan-Meier survival curves were then used to calculate cumulative probabilities of disease reactivation at 5 years after DMT discontinuation for each value of the sum score.
3. In the validation dataset, the performance of the predictive score was evaluated by testing its ability in discriminating patients with low, moderate, and high risk of disease reactivation using Kaplan-Meier survival curves and cumulative probabilities of disease reactivation at 5 years after DMT discontinuation. The statistical significance of intertertile heterogeneity and trend was assessed using log-rank test for trend and a Cox regression model.

Statistical analysis was performed using SPSS 26.0 (IBM, Armonk, NY, USA) and R Statistical Software (version 4.0.0; R Foundation for Statistical Computing, Vienna, Austria). Missing values were handled by multiple (20 times) imputation using the missing not at random approach with pooling of estimates according to Rubin's rules [15]. Censored data were dealt with based on the assumptions of point-censoring (with interval censoring deemed unessential considering the close-meshed follow-up frequency) and independent censoring (implying that time to censoring and survival times are independent). A two-sided p value <0.05 was considered statistically significant.

Standard protocol approvals, registrations, and patient consents

The study was approved by the ethics committees of the Vienna and Innsbruck medical universities (EK Nr: 2323/2019). Written informed consent was obtained from all study participants.

RESULTS

The inclusion processes of the generation and validation datasets are depicted in detail in Figure 1. Table 1 shows the characteristics of both cohorts. There were no significant differences between the generation and validation cohorts at baseline or follow-up.

After analyzing the generation sample by univariate Cox regression, three factors fulfilled criteria (p < 0.2) for entering the multivariable model predicting disease reactivation: age at discontinuation (p < 0.001), MRI activity at discontinuation (p < 0.001), and duration of clinical stability (p < 0.001). In the multivariable analysis, age at discontinuation, MRI activity, and duration of clinical stability remained significantly associated with disease reactivation (Table 2). We assigned integral values expressing the relatively weighted impact of each variable and named the score VIAADISC (Vienna Innsbruck DMT discontinuation score based on age, activity on MRI, and duration in stable course).

The VIAADISC score was highly predictive of disease reactivation (R^2 = 0.811; p < 0.001) with increasing scores on the VIAADISC correlated with increased probability of disease reactivation (Table 3, Figure 2a). Then, we grouped patients according to probability of disease reactivation in the generation dataset as subjects with low risk (i.e., below the 33rd percentile, VIAADISC score 0–1), moderate (i.e., between the 33rd and 67th percentile, VIAADISC score 2), and high risk (i.e., above the 67th percentile, VIAADISC score 3–5) of disease reactivation. The probability of disease reactivation within 5 years after DMT discontinuation was 7.0% (standard error [SE] = 4.8) in the low-risk group, 37.7% (SE = 8.6) in the moderate risk group, and 84.6% (SE = 4.2) in the high-risk group (p < 0.001, Figure 2b). Taking the low-risk group as reference, hazard ratios were 8.9 (95% confidence interval [CI]: 2.0–39.0; p < 0.001) for the moderate risk group and 28.0 (95% CI: 7.0–117; p < 0.0001) for the high-risk group.

In the validation cohort, the VIAADISC score was strongly predictive of disease reactivation as demonstrated by the cox regression (R^2 = 0.749; p < 0.001). The low-risk group displayed a 7.1% (SE = 6.9) probability of disease reactivation within 5 years after DMT

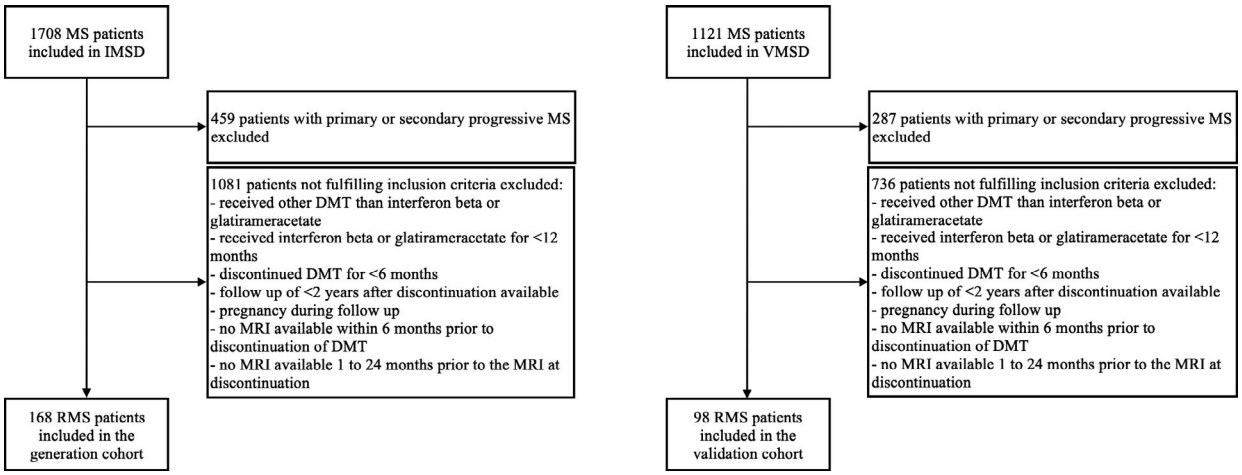

FIGURE 1 Inclusion flowchart of the generation (a) and the validation (b) cohorts. DMT, disease-modifying therapy; IMSD, Innsbruck Multiple Sclerosis Database; MRI, magnetic resonance imaging; MS, multiple sclerosis; VMSD, Vienna Multiple Sclerosis Database.

TABLE 1 Characteristics of the generation and the validation cohorts at DMT discontinuation and at last follow-up

	Generation cohort, *n* = 168	Validation cohort, *n* = 98	*p* value
Baseline			
Demographic and clinical data			
Female[a]	119 (70.8)	68 (69.4)	0.803[d]
Age at onset, years[b]	29.1 (7.6)	29.8 (8.0)	0.478[e]
Age at discontinuation, years[b]	38.0 (12.4)	38.8 (14.1)	0.630[e]
Disease duration at discontinuation, years[b]	9.2 (12.2)	10.1 (13.9)	0.582[e]
Disease-modifying therapy[a]			
Interferon-β-1a i.m.	62 (36.9)	41 (41.8)	0.577[f]
Interferon-β-1a s.c.	35 (20.8)	19 (19.4)	
Interferon-β-1b s.c.	37 (22.0)	18 (18.4)	
Glatiramer acetate	34 (20.2)	20 (20.4)	
Duration of DMT at discontinuation, years[b]	4.1 (6.2)	4.8 (7.0)	0.398[e]
Reasons for DMT discontinuation[a]			
Adverse events	75 (44.6)	43 (43.9)	0.854[f]
Patient's decision	47 (28.0)	27 (27.6)	
Stable disease course	46 (27.4)	28 (28.6)	
EDSS at discontinuation[c]	1.5 (0–5.5)	2.0 (0–6.5)	0.395[g]
Relapse during DMT[a]	82 (48.8)	45 (45.9)	0.596[d]
Duration of clinical stability, years[b]	3.1 (3.2)	3.5 (3.7)	0.354[e]
MRI			
Time between MRI before and at discontinuation (months)[c]	11 (1–24)	12 (1–24)	0.912[g]
Time between MRI at discontinuation and DMT discontinuation (months)[c]	2 (0–6)	2 (0–6)	0.931[g]
MRI activity at discontinuation	98 (58.3)	53 (54.1)	0.500[d]
Increase in T2 lesion load[a]	96 (57.6)	52 (53.1)	0.518[d]
Gadolinium-enhancing lesions[a]	39 (23.2)	21 (21.4)	0.737[d]
Follow-up			
Duration of follow-up after discontinuation (years)[c]	5.0 (2–12)	5.5 (2–12)	0.378[g]
Disease reactivation after discontinuation[a]	90 (53.6)	51 (52.0)	0.809[d]
Relapse after discontinuation[a]	83 (49.4)	47 (48.0)	0.820[d]
EDSS worsening after discontinuation[a]	33 (19.6)	22 (22.4)	0.586[d]
DMT re-starters[a]	66 (39.3)	38 (38.8)	0.934[d]
Time to disease reactivation, years[b]	2.0 (1.5)	1.9 (1.8)	0.724[e]
Conversion to SPMS[a]	10 (6.0)	7 (7.1)	0.702[d]

Abbreviations: DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; i.m., intramuscular; MRI, magnetic resonance imaging; s.c., subcutaneous; SPMS, secondary progressive multiple sclerosis.

[a]Absolute number and percentage.

[b]Mean and 95% confidence interval.

[c]Median and minimum–maximum range.

[d]Fisher exact test.

[e]Independent *t* test.

[f]χ^2 test for trend.

[g]Mann-Whitney *U* test.

discontinuation, which was significantly lower compared to 35.5% (SE = 10.1) in the moderate risk group and 83.2% (SE = 5.4) in the high-risk group (Figure 2c, d).

The proportion of patients converting to secondary progressive MS (SPMS) did not significantly differ between the risk groups, neither in the generation (low risk: 2/24, moderate risk: 3/36, high risk:

TABLE 2 Predictive value of clinical and MRI variables for occurrence of disease reactivation after disease-modifying therapy discontinuation

VIAADISC	HR	95% CI	*p* value	Risk score points assigned
Age at discontinuation				
<45 years	4.3	2.5–7.1	<0.001	2
≥45 and <55 years	2.1	1.4–3.8	<0.001	1
≥55 years	Ref			0
Activity on MRI at discontinuation				
≥3 new/enlarged T2 lesions or ≥1 gadolinium-enhancing lesion	3.9	3.2–4.9	<0.001	2
<3 new/enlarged T2 lesions and no gadolinium-enhancing lesions	Ref			0
Duration of stable disease course				
<4 years	4.4	2.7–8.3	<0.001	2
≥4 and <8 years	2.3	1.6–4.5	<0.001	1
≥8 years	Ref			0

Note: Calculated by multivariate Cox regression model (R^2 = 0.712; p < 0.001).

Abbreviations: 95% CI, 95% confidence interval; HR, hazard ratio; MRI, magnetic resonance imaging; Ref, reference category.

TABLE 3 Probability of disease reactivation after disease-modifying therapy discontinuation stratified according to VIAADISC score

		Generation cohort			Validation cohort		
VIAADISC score		Patients at risk	Disease reactivation–absolute	Probability of disease reactivation[a]	Patients at risk	Disease reactivation–absolute	Probability of disease reactivation[a]
0	Low risk	13	0	0.0 (0.0)	8	0	0.0 (0.0)
1		25	2	9.8 (6.7)	15	1	10.0 (9.5)
2	Moderate risk	39	15	37.7 (8.6)	23	8	35.5 (10.1)
3	High risk	45	33	77.4 (6.8)	28	20	73.2 (8.6)
4		27	22	85.9 (7.3)	16	14	92.5 (7.1)
5		19	18	94.7 (5.1)	8	8	100.0 (0.0)

[a]Percentage (standard error) calculated at 5 years after discontinuation.

5/86; p = 0.841) nor in the validation cohort (low risk: 2/21, moderate risk: 1/22, high risk: 4/48; p = 0.378).

DISCUSSION

In clinical practice, patients frequently ask if and when they can discontinue their DMT, especially those patients, who have not experienced relapses for a long time, have accumulated little or no disability, persistently experience side effects, or are simply growing tired of regularly applying medication. As commonly as these questions arise, there is still very little evidence-based guidance for neurologists counseling patients regarding DMT discontinuation.

Therefore, we aimed to generate and validate a score that is able to quantify the risk of individual RMS patients experiencing disease reactivation after discontinuation of injectable DMT based upon their clinical and MRI characteristics on a baseline evaluation.

The multivariable analysis in the generation sample revealed three factors independently predictive of disease reactivation after DMT discontinuation: (i) age at discontinuation (fourfold increased risk below 45 years and twofold between 45 and 55 years), (ii) MRI activity at discontinuation (fourfold increased risk; defined as three or more new/enlarged T2 lesions or one or more Gd+ lesion), and (iii) duration of clinical stability before discontinuation (fourfold increased risk below 4 years and twofold between 4 and 8 years). Based on this model, a VIAADISC score combining these factors was generated, which was able to stratify patients at low (VIAADISC score = 0–1), moderate (VIAADISC score = 2), and high risk (VIAADISC score = 3–5) of disease reactivation with probabilities of 7%, 38%, and 85%, respectively, 5 years after DMT discontinuation.

The VIAADISC score was reliably attributable to the validation sample with disease reactivation probabilities of 7%, 36%, and 83% for the low, moderate, and high-risk groups. The reliability of the VIAADISC score is underlined by the high goodness-of-fit parameters displayed indicating that at least 75% of the variation in the risk of disease reactivation is explained by the VIAADISC score.

Our results are in line with studies investigating the risk of disease reactivation after DMT discontinuation, which have found

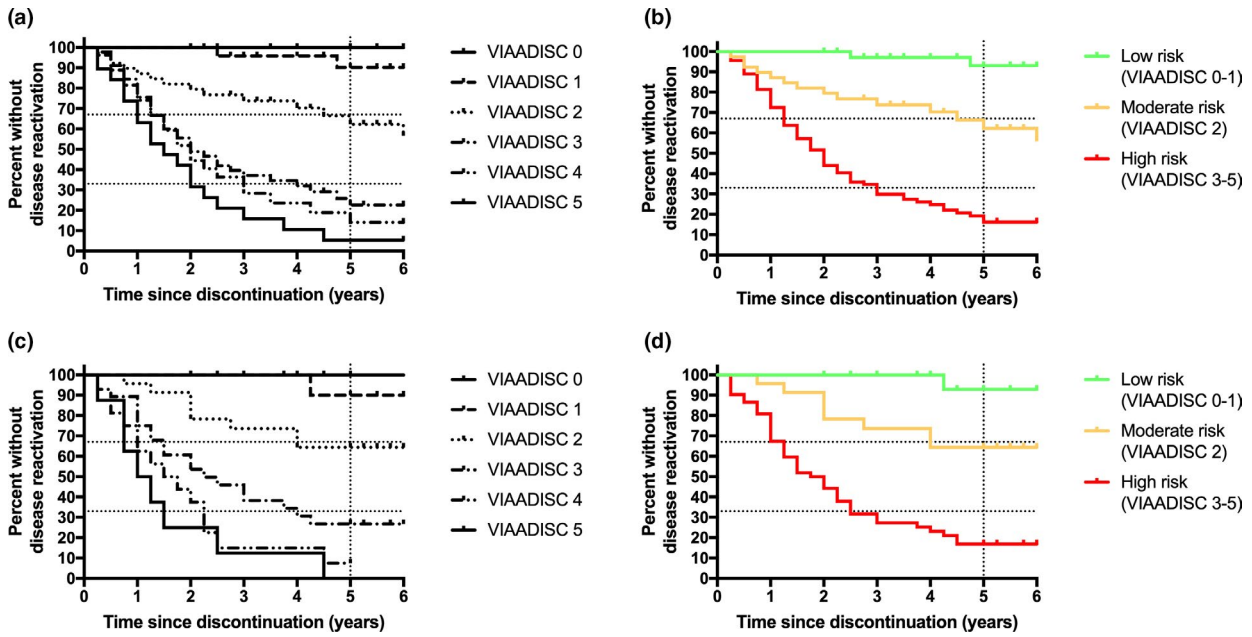

FIGURE 2 Probability of disease reactivation after DMT discontinuation stratified according to VIAADISC score in the generation cohort (a, b) and in the validation cohort (c, d). Vertical dotted line marks the time point 5 years after disease-modifying therapy (DMT) discontinuation used for calculation of probability of disease reactivation. Horizontal dotted lines indicate the 33rd and 67th percentile of probability of disease reactivation. Groups significantly differed in all four graphs ($p < 0.001$, calculated by log-rank test for trend) [Colour figure can be viewed at wileyonlinelibrary.com]

older age at discontinuation (mostly >45–50 years), longer periods without relapses, and absence of MRI activity at discontinuation to be associated with lower likelihood of recurrence of relapse after DMT discontinuation [6–8,16,17]. Adding to this, DMT continuation yields <0.02 quality-adjusted life years above the age of 55 years, which is considered clinically insignificant [18]. Yet, only 12% of patients would consider stopping DMT if their MS was deemed stable, if they are not advised to discontinue by their treating neurologist [4].

Of note, the MRI criterion of three or more new/enlarged T2 lesions or one or more Gd+ lesion was independently associated with the risk of disease reactivation, indicating that MRI carries predictive value in addition to clinical parameters (i.e., age and duration of clinical stability). Although it is self-explanatory that occurrence of new MRI lesions principally reflects MS disease activity, and this cutoff is commonly used in assessing treatment response in MS, it has to be acknowledged that it is not formally validated [14,19]. Thus, we conducted sensitivity analyses using different cutoffs (three or more new/enlarged T2 lesions alone, one or more Gd+ lesion alone, as well as two or more new/enlarged T2 lesions combined with one or more Gd+ lesion), which did not show significant association with the risk of disease reactivation in the multivariable models, neither in the generation nor in the validation cohort. However, in clinical routine, frequency of MRI investigations might be lower than the median 11 to 12 in our cohort depending on accessibility. The predictive value of new T2 lesions is likely reduced with lengthening observation intervals as the number of T2 lesions is expected to increase.

Importantly, disease reactivation rates reported in the literature differ between 5% and 55% depending on applied inclusion criteria either selecting only older patients with long periods of clinical stability or also including patients discontinuing treatment for other reasons such as incompliance or adverse events, where reactivation rates are naturally higher [6–8,16,17,20–27].

The VIAADISC score was specifically designed for determining reactivation risk irrespective of the reason for DMT discontinuation. In this light, we argue that patients with a VIAADISC score ≤1 should be counseled that they can discontinue interferon-β or glatiramer acetate with low risk of recurrence of disease activity, if they want to. However, clinical and MRI monitoring for potential recurrence of disease activity is still mandatory.

As a limitation, it needs to be stressed that only patients discontinuing interferon-β preparations or glatiramer acetate were included. Thus, the VIAADISC score cannot be extrapolated to other DMTs, especially not highly effective drugs such as natalizumab and fingolimod, for which disease reactivation and even rebound is common after discontinuation [28–30].

In addition, due to the small number of patients who have terminated other moderately effective DMTs such as teriflunomide or dimethyl fumarate with a follow-up of more than 2 years, we were also not able to investigate the predictive potential of the VIAADISC score in these DMTs so far. This is an important future direction.

Furthermore, it has to be acknowledged that, although SPMS conversion rates did not differ between the risk groups in our study, the VIAADISC score is not designed to quantify the risk of SPMS conversion.

In conclusion, the VIAADISC score is an easy tool to estimate the risk of disease reactivation in RMS after discontinuation of injectable DMTs and informing patients and neurologists who are deciding if and when to discontinue DMTs.

CONFLICT OF INTEREST

Gabriel Bsteh has participated in meetings sponsored by or received speaker honoraria or travel funding from Biogen, Celgene, Lilly, Merck, Novartis, Roche, Sanofi-Genzyme, and Teva, and received honoraria for consulting from Biogen, Celgene, Roche, and Teva. Harald Hegen has participated in meetings sponsored by or received speaker honoraria or travel funding from Bayer, Biogen, Merck, Novartis, Sanofi-Genzyme, Siemens, and Teva, and received honoraria for consulting from Biogen and Teva. Katharina Riedl reports no disclosures. Patrick Altmann has participated in meetings sponsored by or received speaker honoraria or travel funding from Biogen, Merck, Roche, Sanofi-Genzyme, and Teva, and received honoraria for consulting from Biogen. He received a research grant from Quanterix International and was awarded a combined sponsorship from Biogen, Merck, Roche, Sanofi-Genzyme, and Teva for a clinical study. Michael Auer received speaker honoraria and/or travel grants from Biogen, Merck, Novartis, and Sanofi-Genzyme. Klaus Berek has participated in meetings sponsored by and received travel funding from Roche. Franziska Di Pauli has participated in meetings sponsored by or received honoraria (lectures, advisory boards, consultations) or travel funding from Bayer, Biogen, Celgene, Merck, Novartis, Roche, Sanofi-Genzyme, and Teva. Rainer Ehling has participated in meetings sponsored by or received speaker honoraria or travel funding from Biogen, Böhringer Ingelheim, Celgene, Daiichi Sankyo, Merck, Novartis, Ottobock, and Teva. Barbara Kornek has received speaking honoraria or travel support from Biogen, Celgene, Merck, Novartis, Roche, Sanofi-Genzyme, and Teva and gives advice to Biogen, Celgene, Merck, Novartis, Roche, and Sanofi-Genzyme. Tobias Monschein has participated in meetings sponsored by or received travel funding from Biogen, Celgene, Merck, Novartis, Roche, Sanofi-Genzyme, and Teva. Walter Rinner has received travel funding from Bayer, Biogen, Merck, Novartis, Roche, Sanofi-Genzyme, and Teva. Christiane Schmied has received speaking honoria and travel support from Biogen, Merck, Sanofi-Genzyme, and Teva. Sebastian Wurth has participated in meetings sponsored by or received honoraria or travel funding from Allergan, Biogen, Ipsen Pharma, Merck, Novartis, Roche, Sanofi-Genzyme, and Teva. Anne Zinganell has participated in meetings sponsored by or received speaking honoraria or travel funding from Biogen, Merck, Sanofi-Genzyme, and Teva. Karin Zebenholzer received speaking honoraria or travel grants from Biogen, Novartis, and Sanofi-Genzyme. Tobias Zrzavy has participated in meetings sponsored by or received travel funding from Biogen, Merck, Novartis, Roche, Sanofi-Genzyme, and Teva. Gudrun Zulehner has participated in meetings sponsored by or received travel funding from Biogen, Merck, Novartis, Roche, Sanofi-Genzyme, and Teva. Florian Deisenhammer has participated in meetings sponsored by or received honoraria for acting as an advisor/speaker from Alexion, Almirall, Biogen, Celgene, Merck, Novartis, Roche, and Sanofi-Genzyme. His institution received scientific grants from Biogen and Sanofi-Genzyme. Paulus Rommer has received honoraria for consultancy/speaking from AbbVie, Alexion, Almirall, Biogen, Merck, Novartis, Roche, Sandoz, and Sanofi-Genzyme, and has received research grants from Amicus, Biogen, Merck, and Roche. Fritz Leutmezer has participated in meetings sponsored by or received honoraria for acting as an advisor/speaker for Bayer, Biogen, Celgene, MedDay, Merck, Novartis, Roche, Sanofi-Genzyme, and Teva. Thomas Berger has participated in meetings sponsored by and received honoraria (lectures, advisory boards, consultations) from pharmaceutical companies marketing treatments for multiple sclerosis: Allergan, Almirall, Bayer, Biogen, Biologix, Bionorica, Celgene, MedDay, Merck, Novartis, Octapharma, Roche, Sanofi-Genzyme, Teva, and TG Pharmaceuticals. His institution has received financial support in the past 12 months by unrestricted research grants (Biogen, Merck, Novartis, Sanofi-Genzyme, Teva and for participation in clinical trials in multiple sclerosis sponsored by Alexion, Biogen, Merck, Novartis, Octapharma, Roche, Sanofi-Genzyme, and Teva.

AUTHOR CONTRIBUTIONS

Gabriel Bsteh: study concept and design, patient recruitment, acquisition of data, statistical analysis and interpretation of data, drafting of manuscript. Harald Hegen: patient recruitment, acquisition of data, critical revision of manuscript for intellectual content. Katharina Riedl: patient recruitment, acquisition of data, critical revision of manuscript for intellectual content. Patrick Altmann: patient recruitment, acquisition of data, critical revision of manuscript for intellectual content. Michael Auer: patient recruitment, acquisition of data, critical revision of manuscript for intellectual content. Klaus Berek: patient recruitment, acquisition of data, critical revision of manuscript for intellectual content. Franziska Di Pauli patient recruitment, acquisition of data, critical revision of manuscript for intellectual content. Rainer Ehling: patient recruitment, acquisition of data, critical revision of manuscript for intellectual content. Barbara Kornek: patient recruitment, acquisition of data, critical revision of manuscript for intellectual content. Tobias Monschein: patient recruitment, acquisition of data, critical revision of manuscript for intellectual content. Walter Rinner: patient recruitment, acquisition of data, critical revision of manuscript for intellectual content. Christiane Schmied: patient recruitment, acquisition of data, critical revision of manuscript for intellectual content. Sebastian Wurth: patient recruitment, acquisition of data, critical revision of manuscript for intellectual content. Anne Zinganell: patient recruitment, acquisition of data, critical revision of manuscript for intellectual content. Karin Zebenholzer: patient recruitment, acquisition of data, critical revision of manuscript for intellectual content. Tobias Zrzavy: patient recruitment, acquisition of data, critical revision of manuscript for intellectual content. Gudrun Zulehner: patient recruitment, acquisition of data, critical revision of manuscript for intellectual content. Florian Deisenhammer: patient recruitment, acquisition of data, critical revision of manuscript for intellectual content. Paulus Rommer: patient recruitment, acquisition of data, critical revision of manuscript for intellectual content. Fritz Leutmezer: study concept and

design, patient recruitment, interpretation of data, critical revision of manuscript for intellectual content. Thomas Berger: study concept and design, patient recruitment, interpretation of data, critical revision of manuscript for intellectual content, study supervision.

DATA AVAILABILITY STATEMENT

Anonymized data will be shared by reasonable request from any qualified investigator.

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