A national, multi-center study in Germany to assess implementation of infusion management, treatment satisfaction and quality of life in MS patients receiving alemtuzumab

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ABSTRACT

\textbf{Background:} Alemtuzumab is an anti-CD52 antibody approved for the treatment of relapsing remitting multiple sclerosis (RRMS). The summary of product characteristics (SmPC) provides recommendations on the administration of alemtuzumab to prevent or reduce the risk of serious side effects associated with alemtuzumab infusion, including myocardial ischemia, hemorrhagic stroke, arterial dissection, and pulmonary alveolar hemorrhage. However, real-world implementation of alemtuzumab infusion management recommendations has not been previously assessed.

\textbf{Methods:} Here we provide a large-scale multi-center (in- and outpatient) observational study on alemtuzumab infusion management in daily clinical care in Germany (ALEM08025; INFUSE-MS; NIS-no. 364). Parameters of infusion management - including infusion administration, clinical and laboratory monitoring - were assessed, compared between study centers and the occurrence of infusion-associated reactions (IARs) was documented. Moreover, the TSQM and MSIS-29 questionnaires were used to quantify patient satisfaction and health-related quality of life.

\textbf{Results:} 140 RRMS patients were enrolled in this study. Alemtuzumab infusion regimes (treatment course 1 and 2) were comparable between infusion sites and in accordance with recommendations by the SmPC. Standardization of infusion management was associated with a satisfactory safety profile. IARs were usually mild, headache (13.6%), rash (10.7%), and pyrexia (6.4%) being the most common ones. TSQM and MSIS-29 scores denoted high patient satisfaction and health-related quality of life among RRMS patients treated with alemtuzumab.

\textbf{Conclusion:} In conclusion, our results indicate that infusion management of alemtuzumab is highly standardized and in line with the SmPC. Alemtuzumab treatment and implementation of infusion management recommendations are associated with a satisfactory safety profile regarding the occurrence of IARs, a high patient satisfaction and health-related quality of life as important indicators for the quality of MS care.

1. Introduction

Alemtuzumab (LEMTRADA\textsuperscript{®}) is a selective monoclonal antibody targeting CD52 (Klotz et al., 2012; Moreau et al., 1996; Ruck et al., 2015) approved as disease-modifying therapy (DMT) for adult patients with relapsing-remitting multiple sclerosis (RRMS) (EMA, 2013).

Efficacy of alemtuzumab has proven superior to interferon beta-1a in phase II and phase III randomized clinical trials (CAMMS223 and CARE-
MS I/II trial) (Cohen et al., 2012; Coles et al., 2008; Coles, Alasdair J. et al., 2012). Extension studies have shown long-lasting effects of alemtuzumab treatment (Coles et al., 2017; Coles et al., 2012; Havrdova et al., 2017; Lüdemann et al., 2020; Van Wijmeersch et al., 2020).

Alemtuzumab, as advised by the Summary of Product Characteristics (SmPC), is administered as intravenous infusion in two initial treatment courses (TC; TC 1: five consecutive days and TC 2: three consecutive days). Recommended time between the first and second TC is one year (EMA, 2020). Patients with continued disease activity after TC 2 can receive up to two additional TCs (three consecutive days, respectively) which have yielded beneficial effects on relapse rates, disease activity -assessed by Magnetic Resonance Imaging (MRI) -, and disability (Comi et al., 2019; EMA, 2020).

Rare but severe therapy-associated cardiovascular as well as auto-immune events and infections, which may occur within the first days of infusion until several years after the last dose, elicited temporary restriction for the treatment with alemtuzumab (during the Article 20 procedure, 2019) (EMA, 2019; Klosz et al., 2012; Pfeuffer et al., 2019; Ruck et al., 2015, 2018, 2019). The positive risk-benefit profile led to the release of modified recommendations for the use of alemtuzumab (inpatient treatment of highly active disease manifestation in patients receiving at least one DMT or patients with rapidly evolving disease course) by the EMA in 2020 (EMA, 2020).

While randomized controlled trials are especially valuable during the initial stage of drug development and approval, observational studies can lend further information on drug effectiveness, tolerability in daily clinical routine, outcomes and health-related quality of life (HRQOL). Various studies on efficacy (Frau et al., 2019; Herman et al., 2021; Tuohy et al., 2015), HRQOL (Herman et al., 2021; Ziemssen et al., 2016), infusion reactions (Vukusic et al., 2019), and therapy-associated autoimmune diseases (Cossburn et al., 2011) have been performed so far. Those real-world data provide crucial information on the use, efficacy, and side effects of alemtuzumab treatment in daily routine and therefore present a meaningful complement to randomized clinical trials. However, implementation of infusion recommendations in clinical routine as one important aspect of patient safety has not been assessed so far. Beyond that, clinical and observational studies are often conducted in specialized centers, mainly university hospitals (Cohen et al., 2012; Coles et al., 2008; Cossburn et al., 2011; Frau et al., 2019; Tuohy et al., 2015). Even though a few years after their approval DMTs are also administered in different outpatient facilities, data from those locations are limited and quality control is only partially performed. Given the safety profile of alemtuzumab, a standardized and validated infusion management is especially important to prevent or reduce and immediately recognize infusion-associated reactions (IARs) and serious side effects.

We here present a large-scale multi-center (in- and outpatient) observational study on the real-world implementation of infusion management as substantial aspect of safety and quality control of alemtuzumab treatment in daily clinical care including a post marketing safety analysis, treatment satisfaction, and impact on HRQOL (ALEMIL08025; INFUSE-MS; NIS-no. 364).

2. Methods

2.1. Selection of centers and patients

Study centers were selected according to local requirements for non-interventional studies. Physicians practicing in neurological in- and outpatient clinics in Germany were eligible to take part in this study.

Inclusion criteria for patients were: 1. diagnosis of RRMS according to the revised McDonald criteria (Polman et al., 2011; Thompson et al., 2018), 2. treatment with alemtuzumab, 3. age ≥ 18 years, 4. written informed consent by the patient to participate in the study.

Decision for a treatment with alemtuzumab was made by the patient and the respective physician prior to and independently of enrollment in the study.

Additional information on data collection, management, review, and validation is provided in supplementary methods.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee in Münster, Germany (Ethics Committee of the Board of Physicians of the Region Westfalen-Lippe and of the Westfälische Wilhelms-University Münster; reference number 2016–102-f-S).

2.2. Assessments

Patients were assessed prior to each treatment course with alemtuzumab, on each infusion day, and one year after course two (Fig. 1A). At the baseline assessment (BL1) study eligibility was confirmed, demographic and disease-related information was collected. Variables for the assessment of infusion management are displayed in supplementary Table 1. As observational studies assessing adverse events (AEs; adverse drug reactions (ADRs; injuries as a result of medication use (Bates et al., 1995)) are crucial to an adequate drug safety management, we included a safety analysis in our study. Only AEs that occurred after the start of alemtuzumab (V2) were analyzed. Patient-reported outcomes were assessed using the “Treatment Satisfaction Questionnaire for Medication” (TSQM v1.4) and the “Multiple Sclerosis Impact Scale-29” (MSIS-29 V2) prior to each course of alemtuzumab (Visit [V] 1 and V7) (Fig. 1A).

The TSQM v1.4 is a validated test consisting of 14 items assessing patient satisfaction with side effects, effectiveness, convenience, and global satisfaction. The scale ranges from 0 to 100 in each domain, higher scores indicating higher satisfaction. The MSIS-29 v2 is a disease-specific tool focusing on the physical and psychological implications of MS. The MSIS-29 v2 comprises 29 items subdivided into two subscales. The scales range from 0 to 100, higher scores indicating a higher level of disability (Hobart et al., 2001).

2.3. Statistics

Quantitative data is summarized by mean ± standard deviation (SD). When presenting results for skewed distributions, the inter quartile range (IQR, [25%-percentile; 75%-percentile]) is used.

Qualitative data (e.g. categorical data as sex) were presented by means of (absolute and relative) frequency distributions. The calculation of percentages was based on the valid data per parameter, excluding patients with missing values.

95% confidence intervals of the mean, based on normal approximation, were given for quantitative variables. For qualitative variables, 95% confidence intervals were provided for relative frequencies in each category of a qualitative variable. These were based on exact methods for binomial proportions (Clopper-Pearson type intervals) in case of binary variables and on simultaneous confidence intervals for categorical responses (Goodman type intervals) in case of variables with more than two categories.

3. Results

3.1. Demographics and baseline disease characteristics

147 patients diagnosed with RRMS treated with alemtuzumab at 47 centers in Germany between 01/09/2017 and 09/09/2019 were initially included in our study. Due to restrictions for the use of alemtuzumab in the treatment of RRMS (Article 20 procedure, initiated in April 2019) (EMA, 2019), the targeted number of 800 patients and 200 centers was not reached. Seven patients were excluded as no informed consent was available and/or no alemtuzumab infusion was documented. Thus, the final analysis comprised 140 patients at baseline. Follow-up data for V7 (visit before the start of the second TC) were
available for 87 patients. Therefore, 84 patients started the second treatment course with alemtuzumab. For the majority of patients (n = 130) no documentation was available for V11 (2 years after course 1), therefore, no analysis for V11 was performed (Fig. 1A).

Regarding baseline characteristics, a marked imbalance in sex towards a female predominance (female: 105/140 [75.0%] vs male: 35/140 [25.0%]) was evident. The mean age of patients was 35.2 ± 10.0 years. The time since disease manifestation and first diagnosis was 7.6 ± 6.8 years and 6.9 ± 6.5 years, respectively. The mean EDSS at baseline was 2.6 ± 1.5 (Fig. 1B). The majority of patients had MS relapses in the last 12 months prior to study inclusion (n = 107/138; 77.5%) (Fig. 1C). 106 patients (75.7%) reported MS related symptoms at V1 with fatigue being the most frequent one (n = 69/140; 49.3%), followed by bladder dysfunction (n = 42/140; 30.0%) and spasticity (n = 32/140; 22.9%) (Suppl. tab. 2). 83.6% of patients (n = 117/140) were treated with a DMT prior to alemtuzumab. Accordingly, 16.4% (n = 23/140) of patients were treatment-naive. Interferons (n = 84/140; 60.0%) and fingolimod (n = 55/140; 39.3%) were the most common prior MS medications (Fig. 1D). 96 patients (69.1%) had discontinued the previous MS therapy immediately before the initiation of alemtuzumab treatment, mainly due to insufficient effectiveness (162 of 270 specified reasons for drug discontinuation, multiple entries possible) or AEs (54 of 270 specified reasons for drug discontinuation, multiple entries possible). Other reasons were (intended) pregnancy, lack of compliance, and treatment break. 44.8% (n = 43/96) of those patients reported impairment by adverse reactions of their last MS treatment. Around one fifth of patients had difficulties or inconvenience taking their last MS tab. 3). Even though patients tended to be young adults, a considerable number of patients was unemployed (n = 43/130; 33.1%) or had a part-time employment (n = 19/130; 14.6%) (Fig. 1E).

3.2. Alemtuzumab infusion management

Most sites recruiting RRMS patients were neurological clinics (n = 22/47 [46.8%]; university hospitals: n = 7/22 [31.8%], smaller local hospitals: n = 15/22 [68.2%]) or MS focus practices (n = 20/47; 42.6%). Slightly more inpatient than outpatient infusion cycles were performed for both TCs (Fig 2A). In TC 1, all patients received alemtuzumab infusions on 5 consecutive days, while in TC 2, patients were treated for 3 days, except for one case, where only 2 days were documented. For inpatient courses, the infusion was mainly administered solely supine (TC 1: n = 64/73 [87.7%]; TC 2: n = 44/47 [93.6%]). The main device for infusion administration was the infusion pump, which was used consistently on all infusion days in the majority of cases (TC 1: n = 85/138 [61.6%]; TC 2: n = 59/80 [73.8%] (Fig. 2B). Infusions lasted around 4 h in TC 1 and TC 2 (TC 1: 4.4 ± 0.71 h; TC 2: 4.3 ± 0.61 h) (Fig 2C). There were no major differences in the mean infusion rates across infusion days between TC 1 and TC 2 (TC 1: 26.80 ± 11.28 ml/h; TC 2: 26.40 ± 8.49 ml/h) (Fig 2D). In both TCs, all patients received oral antitherapeutics concomitantly to alemtuzumab infusion. In the majority of cases, antitherapeutics were taken until one month following the first infusion cycle. Furthermore, methylprednisolone, antihistamines, and antipyretics were administered on infusion days, as recommended by the SmPC (EMA, 2020) (Table 1). Full blood cell count was analyzed on 12.8 ± 21.06% (TC 1) and 19.7 ± 26.05% of infusion days (TC 2), C-Reactive Protein (CRP) on 19.0 ± 25.03% (TC 1) and 25.9 ± 28.78% of infusion days (TC 2), serum creatinine on 18.4 ± 24.29% (TC 1) and 26.3 ± 28.65% of infusion days (TC 2). Urinalysis was performed on 9.9 ± 14.58% (TC 1) and 11.6 ± 17.60% of infusion days (TC 2) (Fig 2E). Vital signs (blood pressure [bp], heart rate [hr] and temperature [temp]) were monitored on infusion days in most cases (TC 1: bp: n = 134/140 [95.7%]; hr: n = 134/140 [95.7%]; temp: n = 101/140 [72.1%]; TC 2: bp: n = 80/84 [95.2%]; hr: n = 80/84 [95.2%]; temp: n = 68/84 [81.0%]) (Fig 2F). The mean follow-up duration post infusion was 2 h (TC 1: 113.10 ± 40.77 min; TC 2: 113.20 ± 47.80 min) in both TCs (Fig 2G). Post-infusion vital signs were measured and IARs assessed in most cases (TC 1: bp: n = 121 [86.4%]; hr: n = 121 [86.4%]; temp: n = 93 [66.4%]; IARs: n = 129 [92.1%]; TC 2: bp: n = 74 [88.1%]; hr: n = 74 [88.1%]; temp: n = 66 [78.6%]; IARs: n = 80 [95.2%]). Monitoring of the injection site was performed in around three quarters of patients in both TCs (TC 1: n = 104 [74.3%]; TC 2: n = 66 [78.6%]) (Fig 2H). 84 patients started a second TC, most patients (n = 76/84; 90.5%) exactly 12 months after the first treatment. Reasons for deviation of start time were pregnancy (n = 2), infections (n = 1),...
comorbidities (n = 2), lymphopenia (n = 1), and organizational issues (n = 2).

64 patients (45.7%) suffered from AEs. In total, 244 AEs were documented. The most frequent AEs were headache (n = 19; 13.6%), rash (n = 15; 10.7%), pyrexia (n = 9; 6.4%), and nausea (n = 7; 5.0%) (Fig. 2). 14 patients (10.0%) experienced serious AEs (SAEs) e.g. pyrexia (n = 2), serious rash (n = 1), bradycardia (n = 1), hemorrhage (n = 1), and subacute thyroiditis (n = 1). No death was reported. ADRs were documented in 40 patients (28.6%). Mainly rash (n = 12; 8.6%), headache (n = 10; 7.1%), and pyrexia (n = 7; 5.0%) were noted (Fig. 2).

In seven cases (5.0%) alemtuzumab treatment was discontinued due to AEs (e.g. headache [n = 3; 2.1%], rash [n = 2; 1.4%], pyrexia [n = 1; 0.7%], nausea [n = 1; 0.7%], and bradycardia [n = 1; 0.7%]). SAEs or coinciding AEs (severe bradycardia [n = 1; 0.7%], rash [n = 1; 0.7%], and pyrexia [n = 1; 0.7%]) required an infusion stop and a consecutive withdrawal of alemtuzumab in two patients. Of note, seven patients (5.0%) had MS relapses during the study.

### 3.3. Patient satisfaction and health-related quality of life

Apart from assessing the implementation of infusion management in Germany, we were further interested in patients’ satisfaction with alemtuzumab treatment and its health-related outcomes. To this end,
two different scores (TSQM and MSIS-29) were assessed. Analysis revealed that TSQM scores for effectiveness and global satisfaction were significantly higher at V7 compared to V1 (Fig. 3A, suppl. tab.4) indicating positive effects of alemtuzumab treatment and contentment with therapy in in- and outpatient facilities, respectively. No significant changes were seen for side effects and convenience between V1 and V7. The MSIS-29 scores were lower at V7 in relation to V1 indicating a positive physical as well as psychological impact of alemtuzumab therapy (Fig 3B, suppl. tab. 4).

4. Discussion

Randomized controlled trials assessing efficacy, safety and outcome of alemtuzumab treatment in RRMS patients have yielded promising results (Cohen et al., 2012; Coles et al., 2007, 2008; Coles et al., 2012, 2012; Havrdova et al., 2017). However, clinical trials do not provide information on drug effectiveness, tolerability, long-term effects, and drug management in daily clinical routine. Therefore, observational studies are an essential complement to randomized controlled trials taking into account daily clinical practice.

Studies on different aspects of alemtuzumab treatment - e.g. efficacy, HRQOL, and infusion reactions - have been previously performed (Cossburn et al., 2011; Frau et al., 2019; Tuohy et al., 2015; Vukusic et al., 2019; Willis et al., 2016). However, real-world implementation of infusion management as an important aspect of safety and quality control of alemtuzumab treatment has not been assessed so far. Above that, data from outpatient facilities are very limited as clinical trials and most observational studies focused on specialized centers.

INFUSE-MS presents a large-scale, multi-center (in- and outpatient) observational study on infusion management and implementation according to the SmPC in clinical routine, providing crucial information on quality control, standardization of treatment, and safety monitoring of alemtuzumab infusion.

Taking into account infusion administration and monitoring, our results revealed that alemtuzumab treatment of RRMS patients in Germany is in line with recommendations by the SmPC and comparable between infusion sites. Comparing single parameters with the recommendations by the SmPC, we found that infusion cycles, duration of infusion, infusion rate, pre- and concomitant treatment, as well as monitoring during and post infusion were highly standardized and in accordance with the SmPC. Discrepancies with regard to the current SmPC were noted for the site of infusion as recommendations have changed in 2020 to inpatient administration only as a result of rare but severe therapy-associated events (EMA, 2020).

Association between implementation of infusion management recommendations and adverse events of alemtuzumab treatment has not been previously assessed. We therefore included a safety analysis to evaluate whether standardization of infusion management based on recommendations by the SmPC contributes to patient safety. Safety management of drugs in general presents a crucial aspect of pre-clinical and clinical trials. Apart from safety information from randomized controlled trials, case reports, case series and observational studies provide further information on side effects and safety of alemtuzumab (Bianco et al., 2020; Böhm et al., 2020; Cossburn et al., 2011; Cuker et al., 2020; Holmøy et al., 2019; Obermann et al., 2016; Pfeuffer et al., 2016, 2021; Ruck et al., 2018, 2019; Tuohy et al., 2015; Vukusic et al., 2019). Over the last years, side effects occurred raising safety considerations for different drugs after their approval. In the case of alemtuzumab, reports of rare but severe therapy-associated infections, cardiovascular, and autoimmune events resulted in temporary restrictions for the clinical use of alemtuzumab and modified recommendations for its application (EMA, 2019). Thus, continuous drug safety monitoring is essential in order to guarantee appropriate patient safety (Muraro et al., 2018). Accordingly, we extended our study to include (SAEs and (S)ADRs. SAEs and SADRs occurred in a small minority of patients, no death was reported. IARs - mainly headache, rash, and pyrexia - were the most frequent AEs/ADRs, which is in accordance with observations from controlled clinical trials (Cohen et al., 2012; Coles et al., 2017, 2008; Coles et al., 2012; Havrdova et al., 2017) and observational studies (Vukusic et al., 2019). Taken together, our results indicate that a standardized infusion management is associated with a satisfactory safety profile regarding the occurrence of IARs. Beyond that, lower numbers of SAEs and SADRs, e.g. cardiovascular events, were noted, which could hint towards a contribution of a standardized infusion administration to overall patient safety. However, further studies with long-term follow-up data will be necessary to assess the effect of a standardized infusion management on the safety profile of alemtuzumab.

Apart from a satisfactory risk-benefit profile, patient satisfaction, health-related outcome and quality of life are important components of medical treatments. Dissatisfaction leading to drug discontinuation and insufficient improvement of HRQOL (Devonshire et al., 2011) can have negative effects on a persons’ social and occupational life as well as on the economy. Thus, we included two different questionnaires focusing on patient satisfaction and physical as well as psychological impact of treatment. While there was no significant change in the TSQM score assessing side effects, we observed an increase in subjective effectiveness and global satisfaction as well as a beneficial effect of alemtuzumab therapy on physical and psychological capability. As the majority of patients received prior MS treatment, our results indicate beneficial

Fig. 3. Analysis of patient satisfaction and health-related quality of life A TSQM score assessing patient satisfaction with effectiveness, side effects, convenience, and global satisfaction. Scale ranges from 0 to 100 in each domain, higher scores indicating higher satisfaction. B MSIS-29 score as indicator of physical and psychological capability of RRMS patients treated with alemtuzumab. Scales range from 0 to 100, higher scores indicating a higher level of disability. Two-sided 95% confidence intervals were calculated based on normal approximation. Statistical significance (*) was assumed if the 95% confidence interval did not contain the null value. Higher TSQM score values denote higher satisfaction while higher MSIS-29 score values indicate a higher degree of disability. (MSIS-29: Multiple Sclerosis Impact Scale-29; TSQM: Treatment Satisfaction Questionnaire for Medication; V: Visit)
effects of alemtuzumab treatment after cessation of another DMT, which is in line with a previous study assessing the efficacy and safety of alemtuzumab and fingolimod after natalizumab administration (Pfeuffer et al., 2019).

Even though alemtuzumab is administered intravenously and is therefore expected to cause more inconvenience for patients compared to an oral treatment regime, our results support that patients treated with alemtuzumab are overly satisfied denoting a high HRQOL as often seen with orally administered DMTs (Adam Czapinski, 2014; Le Page et al., 2015).

The main limitations of our study were: 1. the lower recruitment of patients than initially planned as a result of temporary restrictions for the use of alemtuzumab by the EMA (during the Article 20 procedure) and the modified recommendations for its application thereafter (EMA, 2019) and 2. the missing follow-up data for V11 (2 years after course 1) in most cases as well as for further employment status. Previous studies indicate that some side effects of alemtuzumab can occur several years after the initiation of therapy emphasizing the importance of a thorough follow-up, as recommended by the SmPC (Guanera et al., 2017). Given the limited follow-up, our data do not allow for any conclusions regarding the overall long-term safety profile of alemtuzumab. Furthermore, the influence of prior DMTs on (S)AEs and (S)ADRs has not been considered. However, we were still able to recruit a sizeable and representative cohort of RRMS patients and were the first to assess implementation of alemtuzumab infusion management recommendations and its impact on patient safety, satisfaction, and HRQOL. In addition to that, we included patients treated in different in- and outpatient facilities, thus, assessment of infusion management was not only limited to specialized centers but rather included different in- and outpatient facilities. As the majority of patients included in the study was treated in inpatient facilities, our results provide relevant information on the alemtuzumab infusion management according to the modified recommendations by the SmPC after the Article 20 procedure (EMA, 2020).

5. Conclusion

INFUSE-MS presents a large-scale, multi-center (in- and outpatient) observational study on infusion management and implementation of alemtuzumab treatment in clinical routine illustrating a good standardization of MS care irrespective of the treatment site, associated with a satisfactory safety profile regarding the occurrence of IARs and high patient satisfaction as indicators for a high quality of MS care in Germany.

Author contributions

Patients were recruited by treatment centers; data analysis was performed by Sanofi-Aventis Deutschland GmbH; SR performed data visualization; SR, MP and TR wrote the manuscript; SGM supervised the study; TR and NM co-supervised the study; MK, JSK, DT, CN, SP, and LR gave valuable scientific input to the manuscript; SGM conceived and initiated the study. All authors critically revised the manuscript and agree with its contents.

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Data sharing

Further information and requests for resources and pseudonymized clinical data should be directed to and will be fulfilled by Saskia Räuber (Saskia.Janina.Raeuber@med.uni-duesseldorf.de).

Supplementary table legends

Supplementary Table 1: Primary variables for the assessment of alemtuzumab infusion management
( MS: Multiple Sclerosis; TC: Treatment Course)
Supplementary Table 2: Clinical symptoms of RRMS patients at V1
( MS: Multiple Sclerosis; V: Visit)
Supplementary Table 3: Characteristics of prior MS therapy
( MS: Multiple Sclerosis)
Supplementary Table 4: TSQM and MSIS-29 score as indicators of patient satisfaction and physical and psychological impact of alemtuzumab treatment

Number of patients (n), mean ± standard deviation (SD), and 95% confidence interval (CI) are presented for each item. Higher TSQM score values denote higher satisfaction while higher MSIS-29 score values indicate a higher degree of disability.

(MSIS-29: Multiple Sclerosis Impact Scale-29; TSQM; Treatment Satisfaction Questionnaire for Medication; V: Visit)

CRediT authorship contribution statement


Declaration of Competing Interest

SR declares that she has no conflict of interest. MP His research is founded by the German Multiple Sclerosis Society North Rhine-Westphalia (DSMG), Novartis and the program “Innovative Medizinische Forschung” (IMF) of the Medical Faculty of the University of Muenster. MK received travel grants from Merck Serono and Biogen. JSK is a full-time employee of Sanofi-Aventis Deutschland GmbH. DT is a full-time employee of Sanofi-Aventis Deutschland GmbH. SP received travel grants from Sanofi Genzyme and Merck Serono, lecturing honoraria from Sanofi Genzyme, Mylan Healthcare, and Biogen, and research support from Diamed, Merck Serono, and the German Multiple Sclerosis Society Northrhine-Westphalia. LR received travel reimbursements from Merck Serono and Sanofi Genzyme. CN declares that he has no conflict of interest. NM has received honoraria for lecturing and travel expenses for attending meetings from Biogen Idec, GlaxoSmith Kline, Teva, Novartis Pharma, Bayer Healthcare, Genzyme, Alexion Pharmaceuticals, Fresenius Medical Care, Diamed, and BiAL, and has received financial research support from Euroimmun, Fresenius Medical Care, Diamed, Alexion Pharmaceuticals, and Novartis Pharma. TR reports grants from German Ministry of Education, Science, Research and Technology, during the conduct of the study; grants and personal fees from Sanofi-Genzyme; personal fees from Biogen; personal fees and nonfinancial support from Merck Serono; personal fees from Roche; and personal fees from Teva, outside the submitted work. SGM received honoraria for lecturing and travel expenses for attending meetings from Almirall, Amicus Therapeutics Germany, Bayer Health Care, Biogen, Celgene, Diamed, Genzyme, MedDay Pharmaceuticals, Merck Serono, Novartis, Novo Nordisk, ONO Pharma, Roche, Sanofi-Aventis, Chugai Pharma, QuintilesIMS, and Teva. His research is funded by the German Ministry for Education and Research (BMBF), Deutsche Forschungsgemeinschaft (DFG), Else Krönner Fresenius Foundation, German Academic Exchange Service, Hertie Foundation, Interdisciplinary Center for Clinical Studies (IZKF) Muenster, German Foundation Neurology,
Supplementary material

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