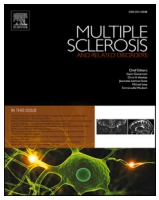
Multiple Sclerosis and Related Disorders 76 (2023) 104770

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard



Original article

Influence of physicians' risk perception on switching treatments between high- efficacy and non–high-efficacy disease-modifying therapies in multiple sclerosis

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ARTICLE INFO

Keywords:
Risk perception
Disease-modifying therapies
Multiple sclerosis
Treatment switch
Non–high-efficacy DMT
High-efficacy DMT

ABSTRACT

Background: The decision of initiating treatment for multiple sclerosis (MS) with a high-efficacy DMT (HE DMT) or non–high-efficacy DMT (non-HE DMT) is influenced by several factors, including risk perception of patients and physicians.
Objective: Investigate the influence of physicians' risk perception on decision-making when switching treatments for MS and the reasons for switching.
Methods: Data were drawn from the Adelphi Real-World MS Disease-Specific Program (a retrospective survey) and analysis included people with RMS identified between 2017– 2021.
Results: Of 4129 patients with reasons for switch available, 3538 switched from non-HE DMT and 591 from HE DMT. Overall, 4.7% of patients were switched treatment by their physicians due to the risk of malignancies and infections including PML risk. The proportion of switches that were made due to the risk of PML were 23.9% in the HE DMT and 0.5% in the non-HE DMT groups. The top reasons for switching were relapse frequency (non-HE DMT vs HE-DMT: 26.8% vs 15.2%), lack of efficacy (20.9 vs 11.7) and increased number of MRI lesions (20.3% vs 12.4%).
Conclusions: Physicians' risk perception of malignancies and infection excluding PML was not a leading factor when switching treatment. The risk of PML was a key factor, especially for switching patients from HE DMTs. In both groups, lack of efficacy was the key contributing factor for switching. Initiating the treatment with HE DMTs may potentially reduce the number of switches due to sub-optimal efficacy. These findings might help physicians to engage more in discussions with patients about the benefit/risk profile of DMTs.

1. Introduction

Multiple sclerosis (MS) is a complex chronic disease of the central nervous system (CNS) characterized by inflammation and neurodegeneration leading to physical and cognitive disability. It is the most common neurological autoimmune disorder among young adults. (Wallin et al., 2019) Presently, there is no definite cure for MS; however, a number of disease-modifying treatments (DMTs) have been developed that reduce relapses and MRI focal lesions and delay disability progression. (McGinley et al., 2021)

DMTs approved for the treatment of MS include various high-efficacy DMTs (HE DMTs) and non–high-efficacy DMTs (non-HE DMT) (Samjoo et al., 2021, Hartung et al., 2021), and have variable benefit-risk profiles that need to be suited to each patient's disease severity and their

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https://doi.org/10.1016/j.msard.2023.104770
Received 10 October 2022; Received in revised form 11 May 2023; Accepted 19 May 2023
Available online 26 May 2023

personal preferences. (Comi et al., 2017) The two main treatment strategies that are well-documented in MS management are escalation and early intensive treatment. (Prosperini et al., 2020) Escalation consists of initiating treatment with non-HE DMTs after diagnosis and then switching to HE DMTs in case of suboptimal response or breakthrough disease (Naismith, 2011) while in the early intensive treatment approach, a HE DMT is initiated shortly after diagnosis. (Ontaneda et al., 2019) Although escalation therapy is the most used approach of treating MS, there is evidence that treating with HE DMT early is beneficial for long-term disease outcomes. (Hartung et al., 2021, Filippi et al., 2021, He et al., 2020, Harding et al., 2019, Buron et al., 2020, Brown et al., 2019, Iaffaldano et al., 2021)

In view of the large array of available DMTs, treatment decisions in MS have become increasingly complex. Previous studies have shown that the decision to initiate a first-line therapy i.e. prescribing a HE DMT or a non-HE DMT can be strongly influenced by an individual's risk perception. (Cocco et al., 2017, Bichuetti et al., 2018, Fox et al., 2019) Risk perception is dynamic and influenced by personal, emotional, social, and experiential factors of both the patient and the neurologist and might differ from one region to another. (Bichuetti et al., 2018) HE DMTs are potentially perceived by physicians as having greater safety concerns (Luna et al., 2020) than non-HE DMTs and thus, are generally reserved for patients with high disease activity or in cases of suboptimal response. (Río et al., 2011) The aim of this study was to investigate the influence of risk perception on physicians' decision when switching treatments for MS and the reasons for switching.

2. Materials and Methods

2.1. Study design and patient population

This study (COMB157G3001) was based on physicians' survey data, drawn from the Adelphi Real-World MS Disease-Specific Program (DSP), a retrospective non-interventional cross-sectional, multi-cohort, and multinational survey of neurologists and their people with MS. The MS DSP asked physicians to complete the survey for the next 10 to 15 consulting patients who met the defined inclusion criteria during the study period. The survey was designed to capture the complete understanding of real-world clinical practice with a series of pre-coded checklists and data fields to be completed for each patient. Physicians who were actively involved in the treatment and management of MS patients, including running specific MS clinics were recruited in the survey. A multi-response questionnaire was developed from a combination of desk research, physician input and other experts in the MS field. The reasons for switch were provided as a pre-coded list to physicians and they were requested to indicate all the reasons for switch that applied (more than one response was allowed), resulting in a more comprehensive view on these multifaceted decisions. If a physician has indicated a specific reason for switch like 'relapse frequency' but also checked 'lack of efficacy', it was counted as 'relapse frequency'. If the physician has not specified the specific reason but mentioned it as 'lack of efficacy', that has been counted for 'lack of efficacy'. Surveys were administered via an online portal that allowed physicians to enter the data collected at the time of patients' consultation and from their documented records. Data were then coded and made available for analysis.

The full methodology of the Adelphi Real-World MS DSP, including limitations, has been previously published. (Anderson et al., 2008) The study population included patients with relapsing-remitting MS (RRMS) and secondary progressive MS (SPMS) aged ≥18 years identified in the Adelphi Real-World MS DSP during Q1 2017 to Q2 2021 (waves VI-IX of Adelphi DSP dataset) with current and previous treatment and whose physician decided to switch their treatment when came for consultation. These criteria did not allow for treatment breaks and included only switches that the physician reported as having no treatment gap. Patients with a diagnosis of primary progressive MS (PPMS) and any other major neurological or psychiatric condition were excluded. For this analysis, eligible patients were classified as per the Samjoo et al publication (Samjoo et al., 2021) into two groups based on the previous treatment, those who were prescribed HE-DMT, and those who were prescribed non-HE DMT (Samjoo et al., 2021) (Fig. 1). HE DMTs identified in the Adelphi database included alemtuzumab, ofatumumab, ocrelizumab, natalizumab, cladribine, and fingolimod, while non-HE DMTs included molecules with moderate or modest efficacy, such as interferons, glatiramer acetate, dimethyl fumarate, and teriflunomide. Analysis was conducted on the global population (including US, UK, European region, France, Germany, Italy, and Spain) and by region.

2.2. Ethical compliance

As the study is based on data collected from a real-world multinational survey of neurologists and their people with MS, it did not require any formal ethical approval. In all study countries, the DSP fieldwork teams adhered to the national data collection regulations as mentioned in the Anderson et al publication. (Anderson et al., 2008) The Disease Specific Programme was conducted in accordance with the European Pharmaceutical Market Research Association (EphMRA) Code of Conduct. The study protocol (reference number AG AG8651) was submitted to the Western Institutional Review Board, and an ethics waiver was provided as it was determined that ethics approval was not required for this study. All data were collected following procedures with ethics committee approval, and data were fully de-identified prior to receipt by Adelphi Real World. The respondents provided informed consent for the use of their anonymized and aggregated data for research and publication in scientific journals. All data, methodology, materials, and data analysis, that support the findings of this survey are the intellectual property of Adelphi Real World. As such no administrative permissions were required to access and use the data.

2.3. Primary endpoint

The proportion of patients who were switched based on physician's risk perception (infections, malignancies, others) in patients treated previously with non-HE DMT and HE DMT.

2.4. Secondary endpoints

Secondary endpoints included: (1) Reasons for switching treatment in the non-HE DMT and HE DMT groups; (2) the proportion of patients who switched due to lack of efficacy, due to new or enlarging lesions on magnetic resonance imaging (MRI), increase in the frequency and/or severity of the relapses, progression in physical disability measured by Expanded Disability Status Scale (EDSS) or patient compliance issues between the groups; and (3) proportion of patients who changed the treatment group versus patients who continued in the same treatment group.

2.5. Statistical analysis

Adelphi team performed all analyses, and summary statistics was provided by groups and overall. Continuous endpoints were summarized using standard summary statistics (n, mean, standard deviation [SD], median, 25th and 75th percentiles, minimum, maximum and IQR), while categorical endpoints were summarized using frequency counts and percentages. A missing category was only presented when any patients reported missing data. Reasons for treatment switch, including risk perception (malignancies/infections) were compared between those who were prescribed with HE DMT and non-HE DMT. The risk of infection was assessed with and without including the risk due to PML. Fisher's exact test was used to compare these outcomes, and a p-value of less than 0.05 was considered statistically significant (indicating an association between HE DMT/non-HE DMT prescription and the outcome

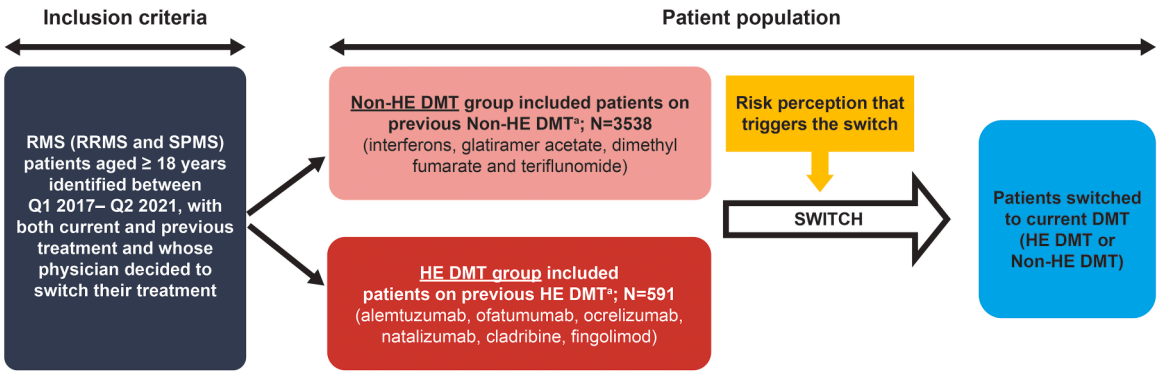

Fig. 1. Patient population and inclusion criteria a The classification of HE DMT and non-HE DMT is based on Samjoo IA, et al. publication cited below. DMT, disease-modifying therapy; DSP, Disease-Specific Program; HE DMT, high-efficacy DMT; MS, multiple sclerosis; non-HE DMT, non–high-efficacy DMT; Q, quarter; RMS, relapsing MS; RRMS, relapsing remitting MS; SPMS, secondary progressive MS.

in question). Fisher's exact test is part of a class of tests that produces exact p-values, rather than p-values that become exact in the limit as the sample size tends to infinity. This is particularly advantageous when reported proportions are low. No adjustments were made for multiple comparisons. The p-values for the baseline characteristics were calculated using t-tests, Fisher's exact test and Mann-Whitney test (EDSS only). Considering the annualized relapse rates in the Danish Multiple Sclerosis Registry of 0.22 for highly-effective DMT and 0.32 for moderately-effective DMT, the expected proportion of the patients who switched the DMT due to lack of efficacy were expected to be around 0.22 (0.19–0.27) for HE DMT and 0.32 (0.28–0.37) for non-HE DMT (Chalmer et al., 2019). For the groups of 300 patients each, the expected power exceeded 80%, which provided a reasonable robustness of the comparisons.

3. Results

3.1. Study population

In the Adelphi MS DSP data set, data were available for 17,307 patients. Of those, data for previous DMT were available for 4361 patients (Previous non-HE DMT, n=3768; 86.4%; Previous HE DMT, n=593; 13.6%) and the reason for switching from previous DMT was provided by physicians for 4129 patients. Detailed patient disposition is presented in the supplementary Table S1. No differences were found in terms of age (non-HE DMT, 42.0 [standard deviation: 11.1] and HE DMT, 42.5 [10.4]) and sex (majority females [non-HE DMT, 64.8% and HE DMT, 69.8%]) between the two groups. Most of the patients had current MS diagnosis of RRMS (non-HE DMT, 86.1% and HE DMT, 72.0%). Patients in the HE DMT group had higher unemployment rate (10.9% vs 7.9%, p=0.0194), longer time since initial MS diagnosis (9.5 years vs 7.9 years, p<0.0001), higher current median EDSS score [3 (2.0, 4.5) vs 2.5 (1.5, 3.5), p<0.0001] and a higher percentage of patients with severe disease compared with patients in the non-HE DMT group. MS-related hospitalizations in the last 12 months were lower in the non-HE DMT group compared with HE DMT group (non-HE DMT, 7.2%; HE DMT, 15.1%, p<0.0001; Table 1).

3.2. Physicians' risk perception of malignancies and infections as a reason for switching treatment

The perceived risk of malignancy (p<0.0001), and infection including PML (p<0.0001) were significantly higher in patients treated with HE DMTs versus non-HE DMTs. Despite this high physicians' perceived risk, very few patients were switched due to the risk of malignancies in both groups (non-HE DMT, 0.1% vs. HE DMT, 1.5%); Fig. 2).

When the risk of PML was not considered, the perceived risk of

Table 1
Demographics and clinical characteristics.

Variable	Overall N=4361	Previous non-HE DMT N=3768	Previous HE DMT N=593	p-value
Age (years), mean (SD)	42.1 (11), n=4361	42.0 (11.1), n=3768	42.5 (10.4), n=593	0.3337[a]
Female	65.5, n=4361	64.8, n=3768	69.8, n=593	0.0178[b]
Current EDSS, median (IQR)	2.5 (1.5, 4.0), n=3907	2.5 (1.5, 3.5), n=3366	3 (2.0, 4.5), n=541	<0.0001[c]
Current diagnosis: RRMS	84.2, n=4361	86.1, n=3768	72.0, n=593	<0.0001[b]
Current diagnosis: SPMS	15.8, n=4361	13.9, n=3768	28.0, n=593	
Time since initial MS diagnosis (years), mean (SD)	8.1 (6.1), n=3640	7.9 (6.0), n=3144	9.5 (6.4), n=496	<0.0001[a]
Duration of previous treatment (years), mean (SD)	3.3 (3.2), n=3232	3.3 (3.3), n=2753	3.0 (2.4), n=479	0.0278[a]
Patients improving	6.9, n=4360	7.1, n=3767	5.1, n=593	0.0662[b]
Patients deteriorating	26.4, n=4360	25.2, n=3767	34.4, n=593	<0.0001[b]
Inpatient	2.6, n=4361	2.4, n=3768	3.9, n=593	0.0358[b]
Outpatient	97.4, n=4361	97.6, n=3768	96.1, n=593	
Working full time	47.7, n=4304	49.0, n=3718	39.4, n=586	<0.0001[b]
Unemployed	8.3, n=4304	7.9, n=3718	10.9, n=586	0.0194[b]
Living in a nursing home	0.3, n=4361	0.2, n=3768	0.5, n=593	0.2168[b]
Caregiver responsible for patient's daily needs	21.5, n=4276	20.6, n=3700	27.3, n=576	0.0004[b]
Hospitalisation[d] in the last 12 months related to MS	8.2, n=3632	7.2, n=3147	15.1, n=485	<0.0001[b]

aP-values calculated using T-test, bP-values calculated using Fisher's exact test, cP-values calculated using Mann-Whitney test, dMS related hospitalizations only and do not include consultations related to infusion of HE therapies
Data presented as % unless specified otherwise. "n" denotes the number of patients for whom the data was available and included for analysis for a specific variable; the data for some of the variables was missing as it was not available in the physician's case notes when the data were captured.
DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; HE DMT, high-efficacy DMT; IQR, interquartile range; non–HE DMT, non–high-efficacy DMT; MS, multiple sclerosis; SD, standard deviation.

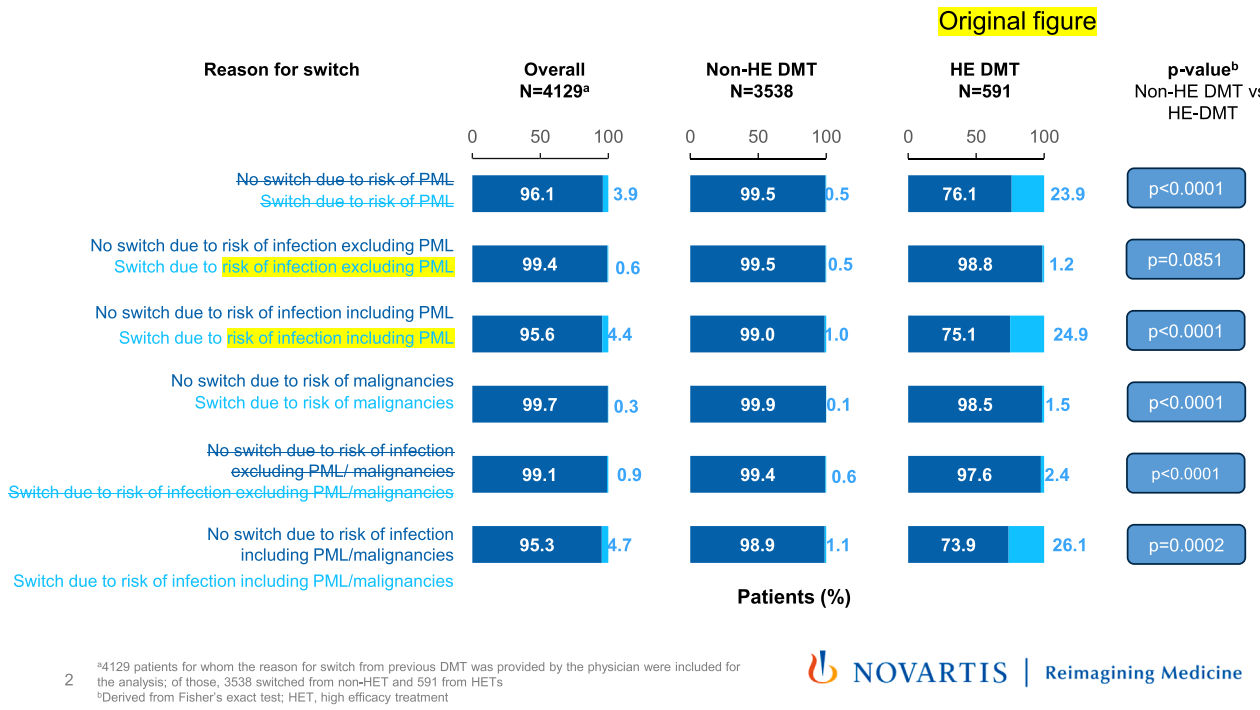

Fig. 2. Proportion of patients who were switched based on physicians' risk perception for malignancies, infections or malignancies and infections [a]4129 patients for whom the reason for switch from previous DMT was provided by the physician were included for the analysis; of those, 3538 switched from non-HE DMTs and 591 from HE DMTs[b] Derived from Fisher's exact test DMT, disease-modifying therapy; HE, high-efficacy; non-HE, non–high-efficacy.

infection was similar in both HE DMT and non-HE DMT groups (p=ns). The perceived risk of PML, when counted, played a significant role for switching in the HE DMT group (HE DMT, 23.9% vs non-HE DMT, 0.5%; p<0.0001). Analysis by region did not show any significant difference when compared with the global results (data not shown).

3.3. Other reasons for switching treatment

The top reasons for switching in the overall population were relapse frequency (25.1%), lack of efficacy (reason not specified; 19.6%) and increased number of lesions (19.1%). . The top three reasons for switching the treatment in the non-HE DMT group were relapse frequency (26.8%), lack of efficacy (reason not specified; 20.9%) and patient request (20.6%) while in the HE DMT group, the top reasons were risk of PML (23.9%), new T2 or gadolinium-enhancing (Gd+) lesions (17.9%) and progression in EDSS (15.1%). The most common reasons (>10% in any group) for switching treatment are presented in Fig. 3. The percentage of patients who switched the treatment due to lack of efficacy was significantly higher in the non-HE DMT group (66.0%) in comparison with the HE DMT group (55.0%; p<0.0001). Relapse

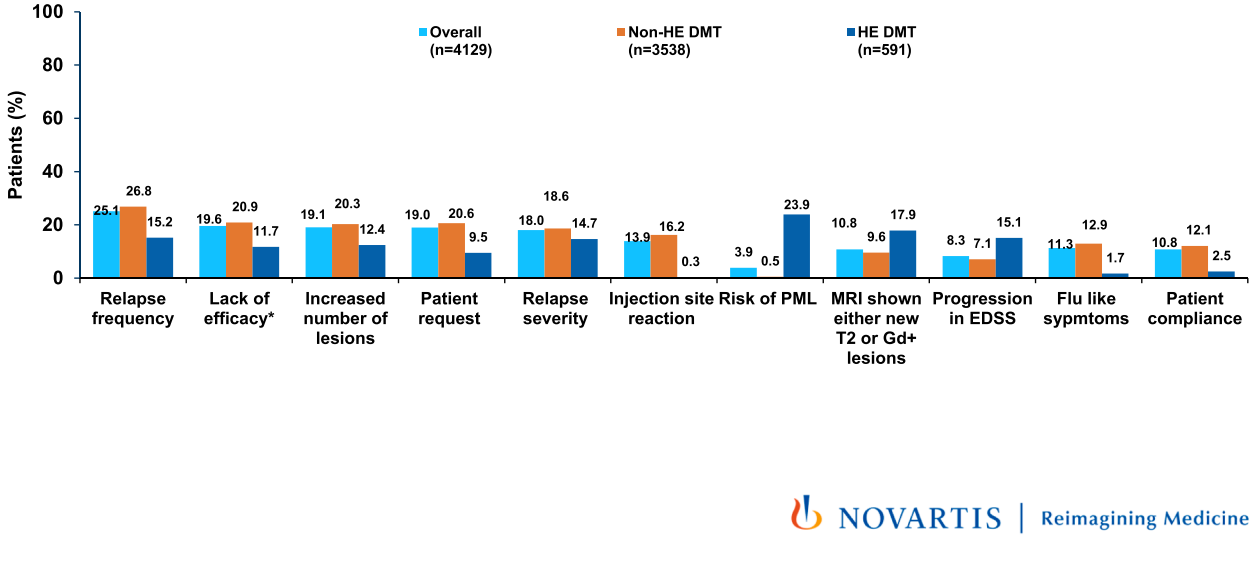

Fig. 3. Most common reasons (>10% in any group) for switching treatment Risk of PML is largely contributed by natalizumab DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; HE DMT, high-efficacy DMT; non-HE, non–high-efficacy; PML, progressive multifocal leukoencephalopathy.

frequency, lack of efficacy (reason not specified) and increased number of lesions are the main factors influencing treatment switching, especially in the case of non-HE DMTs when compared with HE DMTs .

3.4. Proportion of patients who changed the treatment group versus patients who continued in the same treatment group

The proportion of patients who switched from the non-HE DMT to the HE DMT was 45.4% and 54.6% of patients continued in the non-HE DMT group. The most common HE DMT switched to was fingolimod (19.1%) followed by natalizumab (14.3%), ocrelizumab (6.5%), and alemtuzumab (2.0%, Fig. 4a). The proportion of patients who switched from HE DMT to non-HE DMT was 28.7% and 71.3% continued in the HE DMT group. The most common non-HE DMTs switched to were fumarates (13.0%) followed by teriflunomide (3.9%), glatiramer acetate (3.9%), and interferon beta-1a (2.5%, Fig. 4b).

4. Discussion

Treatment decisions in MS are strongly influenced by an individual's risk perception, (Cocco et al., 2017) choice of available DMTs, and several other factors. The present study investigated the influence of risk perception on physicians' decision when switching treatments for patients with MS. The findings of this study show that efficacy-related reasons were the common reasons for switching in both HE DMT and non-HE DMT groups. When the analysis was focused on the risk of infection, the physicians' perceived risk of infections including PML was the leading cause of switch from HE DMT (24.9%) compared to non-HE DMT (1.0%). On the other hand, though the perceived risk of malignancies was significantly higher in the HE DMT versus non-HE DMT, very few patients were switched for risk of malignancy in these groups (HE-DMT, 1.5%vs. 0.1% in the non-HE DMT).

The overall leading cause of treatment switch from any previous DMT was relapse frequency (25.1%). This observation is in line with Sacca et al (Saccà et al., 2018) who mentioned that "Poor efficacy" is the more frequent cause of switch compared to safety/intolerance issues, and with Patti et al (Patti et al., 2020) who highlighted that efficacy remains the main driving force behind switching behavior. Nonetheless, we want to emphasize that patient safety and tolerability are of utmost importance, and these results highlight the urgency of the physician to control this devastating disease.

Of note, the fourth most common reason for treatment switch in the non-HE DMT group was patient request (20.6%) which may be suggestive of tolerability issues or lack of compliance to previous therapy.

Most patients (86.4%) were previously on a non-HE DMT versus HE DMT (13.6%), indicating that most of the neurologists still prefer the traditional treatment escalation approach and reserve HE DMTs for severe disease or later disease stage (i.e., after a suboptimal response to non-HE DMTs). This could explain, as well, that more patients switched from non-HE DMT to HE DMT (45.4%) than from HE DMT to non-HE DMT (28.7%).

The patients in the HE DMT group had longer "time since initial MS diagnosis," higher current EDSS score, lower proportion of patients with RRMS, higher inpatient status, higher unemployment rate, and a higher proportion of patients in this group required caregiver assistance. These differences may indicate that patients in the HE DMT group had already a more severe disease or may have been prescribed with first-line therapies prior to initiation of HE DMT. Thus, patients may have lost important time at the beginning of the disease where a large proportion of neuroinflammation and eventual disability accrual may occur.

The availability of multiple HE DMTs, an increased understanding of the natural history of MS, and a growing amount of data suggest that initiation of MS treatment with HE DMT has a beneficial long-term impact on the neurological impairment and lower the risk of EDSS worsening and relapses when initiated early in the disease course. (Filippi et al., 2021, Wiendl et al., 2021, Schmierer et al., 2021, Spelman et al., 2021, Anderson et al., 2008, Brown et al., 2019)

Our study suffers from few limitations due to the observational and retrospective nature of the design which could lead to inaccuracies in data. As the data were derived using a survey-based methodology, it may have excluded relevant types of patients who were not receiving treatment at the time of the study. Moreover, data in the Adelphi DSP data set may be subject to some selection bias. The data were captured at the time of consultation and therefore patients who consult less frequently are less likely to occur in the data set. In addition, the fact that physicians could indicate multiple reasons for switch that makes the data reflective of real-world multifactorial decision-making, however it does make the data more difficult to interpret clearly. This is typical of any consultation-based collection and one should be cautious when generalizing the results of this study. Our study has classified the available MS DMTs into HE DMT and non-HE DMT categories on the basis of the Samjoo et al publication (Samjoo et al., 2021); however, authors recognize that other classification approaches may categorize the DMTs differently. Authors also acknowledge that different countries may have different re-imbursement guidelines or varying real-world access realities which may also be a factor in the choice of initial treatment; however, the current study was not aimed at investigating the implications of such scenarios.

In conclusion, our study results show that physicians' risk perception of malignancies and infection excluding PML was not a leading factor for switching treatment. However, when the risk of PML is considered, the risk of infection seemed to be a key factor for switching in the HE DMT group. The common reason for treatment switch in both groups was lack of efficacy, perhaps related to the fact that the escalation approach continues to be the dominant approach in MS. Considering that switching due to risk of infection excluding PML or malignancies is low, treatment initiation with HE DMTs as first-line can be considered where the chosen HET is less likely to cause PML or where the PML risk can be

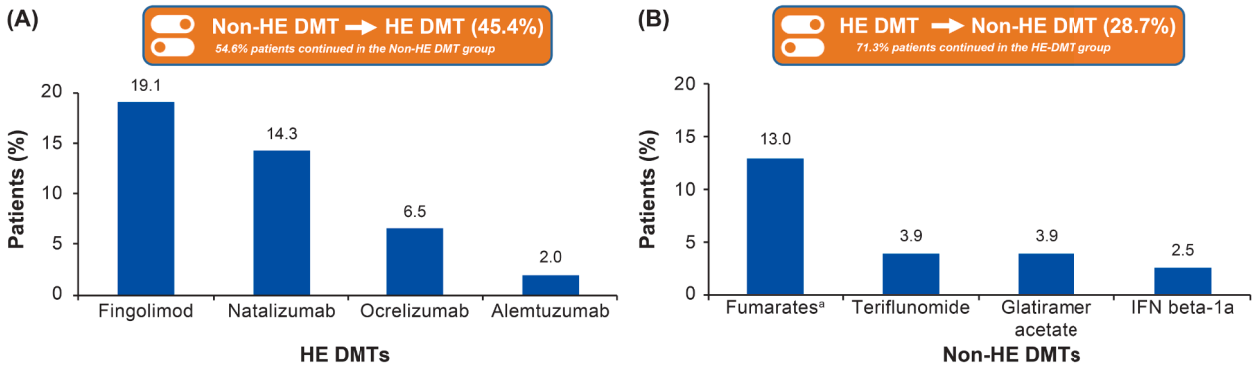

Fig. 4. Most common current DMTs switched to from previous DMT [a]This includes dimethyl fumarate and diroximel fumarate DMT, disease-modifying therapy; HE, high efficacy; non-HE, non–high-efficacy.

carefully managed.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

CRediT authorship contribution statement

Gustavo Seifer: Conceptualization, Data curation, Writing – review & editing. **Tarunya Arun:** Data curation, Writing – original draft, Writing – review & editing. **Carlos Capela:** Writing – original draft, Writing – review & editing. **Guy Laureys:** Data curation, Writing – original draft, Writing – review & editing. **Eddie Jones:** Data curation, Writing – original draft. **Patricia Dominguez-Castro:** Conceptualization, Data curation, Writing – review & editing. **Rainel Sanchez-de la Rosa:** Conceptualization, Data curation, Writing – review & editing. **Simone Hiltl:** Conceptualization, Data curation, Writing – review & editing. **Pietro Iaffaldano:** Data curation, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

Tarunya Arun has nothing to disclose.

Carlos Capela has received consulting fees from Janssen, Merck and Roche, has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Almirall, Biogen, Bristol Myers Squibb, Janssen, Merck, Novartis, Roche, Sanofi-Genzyme and Teva, has received support for attending meetings and/or travel from Almirall, Bayer, Merck, Novartis, Roche, Sanofi-Genzyme and Teva, has participated on a Data Safety Monitoring Board or Advisory Board for Biogen, Janssen, Merck, Novartis, Roche and Sanofi-Genzyme.

Guy Laureys and/or his employer (UZ Ghent) have received financial compensation for congress attendance, consultancy, research and education by Almirall, Biogen, Celgene, Bristol Myers Squibb, Novartis, Roche, Sanofi, Teva.

Pietro Iaffaldano and/or his institution has received medical writing support for present manuscript from Novartis, has received grants from Novartis, Biogen and Roche; has received consulting fees from Novartis, Biogen, Sanofi, genzyme, BMS, Merck and Roche; has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Roche, Biogen, Sanofi and Merck; support for attending meetings and/or travel from Biogen, Sanofi and Merck and participated on a data safety monitoring board or advisory board for Novartis, Biogen, Sanofi, Genzyme, BMS, Merck and Roche.

Eddie Jones is an employee of Adelphi Real World. Adelphi Real World received funds from Novartis in exchange for access to the MS DSP data set that was used for analysis. Eddie Jones did not receive any funding directly from Novartis.

Patricia Dominguez-Castro, and Simone Hiltl are employees of Novartis Pharma AG.

Gustavo Seifer was an employee of Novartis Pharma AG at the time of study design, execution, interpretation and submission.

Rainel Sanchez-de la Rosa was an employee of Novartis Pharma AG at the time of study design and execution.

Acknowledgments

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published. All authors are responsible for intellectual content and data accuracy. We thank Arshjyoti Singh and Sreelatha Komatireddy (Novartis Healthcare Ltd, Hyderabad, India) for providing medical writing support, which encompassed a literature search, writing of the manuscript, formatting, referencing, preparation of tables and figures per the journal guidelines, and incorporating the authors' revisions and finalising the draft for submission, all under the direction of the authors. This assistance was funded by Novartis Pharma AG, Basel, Switzerland.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2023.104770.

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