

Neoplasm Reports in Patients with Multiple Sclerosis Treated with Disease-Modifying Therapies: An Analysis of the EudraVigilance Database

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Abstract

Background

Multiple sclerosis (MS) is an inflammatory demyelinating disease affecting millions of people worldwide. Recently, numerous new high-efficacy treatment agents have been authorised reducing the MS relapses rates and slowing down the disease progression. Simultaneously, due to their immunosuppressive properties and risk of various pathologies, including carcinogenesis, concerns on drugs safety appeared. We aimed to assess the risk of carcinogenesis in MS patients treated with different disease modifying therapies (DMTs) available in Europe, based on the spontaneous reports from EudraVigilance database.

Methods

Data collected in Eudravigilance database till the end of April 2024 was analyzed.

Disproportionality analysis was conducted using reporting odds ratios (RORs) and proportional reporting ratios (PRRs), together with 95% confidence intervals (CIs) and chi-square tests.

Results

A total of 12,565 neoplasm-related adverse drug reaction (ADR) reports involving multiple sclerosis DMTs were identified. Five DMTs met the ROR-based criteria ($ROR > 1$, lower 95% CI > 1 and at least three reports): fingolimod ($ROR = 1.50$), interferon beta-1a ($ROR = 1.35$), natalizumab ($ROR = 1.29$), ocrelizumab ($ROR = 1.09$), and mitoxantrone ($ROR = 8.63$). However, mitoxantrone was the only DMT that met all five predefined signal criteria, including the PRR threshold ($PRR \geq 2$), with a PRR of 5.55, indicating a marked disproportionality in neoplasm reporting.

Conclusion

Results suggest that MS DMTs are not associated with significantly increased number of reports on neoplasm and cancer development, excluding mitoxantrone. As number of DMTs in MS constantly increases further monitoring might be required.

Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating and neurodegenerative disease of the central nervous system (CNS). In 2023 number of patients reached 2,9 million worldwide.[1] Typically in women a prevalence/incidence rate of the disease approximately double or even triple the men.[2] The disease typically affects young people between the ages of 30 and 40 but may start at childhood and in elderly. [3] First disease modifying drugs (DMTs) in MS such as interferons and glatiramer acetate were introduced in early nineties. In recent years, a number of high-efficacy treatment agents (HETA) have been registered such as for example anti-CD20 antibodies with the aim of significantly reducing MS relapses rates, MRI activity, and slowing down the disease progression.[4] Simultaneously concerns on drugs safety appeared. HETA has been demonstrated to exert an excessive immunosuppressive effect, which may be further associated with an elevated risk of various pathologies, including carcinogenesis. Shortly after such suspicions appeared it was hypothesized that other DMTs with immunosuppressive properties may also be associated with an elevated risk of cancer development in patients with MS.

Although numerous studies have attempted to further characterize cancer risk factors in the MS population, the available evidence remains inconclusive. Early studies suggested an increased risk of cancer, particularly for brain and urinary tract malignancies.[5–7] However, more recent population-based cohort studies, and systematic reviews have not confirmed these findings. [8–11] A 2020 meta-analysis found no evidence of an increased overall cancer risk in patients with MS compared to the general population. [12] New reports continue to emerge suggesting differences in the incidence of certain cancers among patients with MS compared to the general population.[13, 14] As indicated by numerous studies, advancing age is the most significant risk factor for cancer in general, as well as for a multitude of specific cancer types. As patients

grow older, there is an increased likelihood of the presence of comorbidities, which have the capacity to exert a detrimental effect on the progression of the disease and to impose limitations on available therapeutic strategies. Older people have an increased susceptibility to infections, a weakened response to vaccination and an elevated risk of developing cancer, which is believed to be a result of immunosenescence. Immunosenescence is generally associated with a decrease in the number of naive T and B cells, NK cells and disruption of the pro- and anti-inflammatory balance by changes in the production of cytokines. In fact, ageing of the immune system has a complex network of underlying causes which include not only natural mechanisms of senescence but also chronic disorders, lifestyle, environmental and epigenetic factors, and infections.[15] Moreover, immunosenescence is a significant factor affecting the course of MS, as well as the safety of DMTs.[15]

Age is a well-established risk factor for cancer in patients with multiple sclerosis (MS), the risk of malignancy increases with aging and is particularly elevated in individuals over 60 years. Moreover, a higher cancer risk has been reported both in patients with later disease onset and in those with longer disease duration; both associations most likely reflect greater attained age rather than independent effects of the age at onset or of disease duration itself.[14, 16]

Recent studies have indicated a heightened prevalence of multiple sclerosis (MS) among the elderly, particularly after the age of 50.[17] This phenomenon, termed late-onset MS (LOMS), has been observed affecting up to 12% of certain demographic groups.[18] To date, no clinical study has focused primary on the efficacy and safety of DMTs in older patients with MS. Clinical trials have also rarely included patients over the age of 55 years or those with a disease duration exceeding 10 years who are generally at higher risk of neoplasm comparing to younger population. In order to assess the risk of cancer development in patients treated with DMTs, it is necessary to undertake longer-term observations in clinical practice. Significant source of information might be spontaneous reporting. To assess the real risk of carcinogenesis robust postmarketing pharmacovigilance observations are needed. EudraVigilance database serves as source of information gathered in European countries on suspected adverse events of drugs. It was initially launched by European Medicines Agency in 2012 but essentially changed in 2017 and provides public access to reports of “suspected adverse drug reactions (ARDs)” for authorized medicines in the European Economic Area.[19] These publicly available reports are crucial for assessing the safety of the medicine in real-world conditions.

With the aim of getting an idea of the risk scale of carcinogenesis in MS patients treated with different DMTs available in Europe, we analyzed the data collected in EudraVigilance database focusing on the reported cases of neoplasms in MS patients’ population.

Materials and Methods

We designed a database-related pharmacovigilance study to analyze the reporting rate of neoplasm-related ADRs in MS patients treated with different DMTs.

EudraVigilance database was searched, for data collected up to the end of April 2024, to identify reports of neoplasms of any type among all adverse event reports for MS DMTs.

The outcomes were defined according to Medical Dictionary for Regulatory Activities adverse events including. “Adenocarcinoma”, “Adenoma”, “Benign”, “Blastoma”, “Cancer”, “Cancerous”, “Carcinoid”, “Carcinoma”, “Dysplasia”, “Fibroma”, “Granuloma”, “Haemangioma”, “Langerhans' cell histiocytosis”, “Leiomyoma”, “Lesion”, “Leukaemia”, “Leukoplakia”, “Lipoma”, “Lymphoma”, “Lymphoproliferative syndrome”, “Malignacy”, “Malignant”, “Melanocytic naevus”, “Melanoma”, “Meningioma”, “Meta”, “Metaplasia”, “Metastases”, “Myelodysplastic syndrome”, “Myeloma”, “Neoplasm”, “Neuroblastoma”, “Neuroendocrine”, “Polycythaemia vera”, “Precancerous”, “Proliferative”, “Richter's syndrome”, “Sarcoma”, “Tumor”, “Tumour”. As well as different combinations of said terms, for example: a search for the term “Blastoma” returned also “Glioblastoma”; “Cancer” identified “Lung cancer” and other terms paired with the word “Cancer”; “Carcinoma” returned “Squamous cell carcinoma”, as well as “Carcinomatosis” etc.

The reports of the above events were analysed in relation to the following types of DMTs:

1. Interferons: interferon beta-1a (INF beta-1a), including pegylated form of the drug (pegIFN-beta-1a), interferon beta-1b (INF beta-1b)
2. Fumarates (fumaric acid esters): dimethyl-fumarate,
3. Sphingosine-1-phosphate receptor modulators: fingolimod, ozanimod, siponimod, ponesimod
4. Monoclonal antibodies: ocrelizumab, ofatumumab, natalizumab, alemtuzumab
5. Others: glatiramer acetate, teriflunomide, cladribine, mitoxantrone.

Some drugs have mutual indications, including multiple sclerosis and e.g. leukaemia and were registered in different time-points for different indications. Only multiple sclerosis was taken into considerations. As an indication for the drug the following terms were searched: "Multiple sclerosis", "Sclerosis multiplex", "MS", "SM", "Clinically isolated syndrome", "CIS".

Due to the limitation of the data, that can be exported from the Eudravigilance database the age cohort of the patients cannot be thoroughly analyzed. Reports from all age groups available in the database (18–64 years; 65–85 years; more than 85 years; and age not specified) were therefore included without further stratification, and the analysis of demographic characteristics was restricted to the sex of the reported patients.

Eudravigilance resources were analyzed with RStudio. Since Eudravigilance database is based on spontaneous reporting of ADRs, it is impossible to determine the total population of patients exposed, moreover since the reporting is spontaneous and voluntary not all ADRs are reported and recorded in the database.

Therefore, disproportionality analyses of specific drug–ADR pairs are needed to identify potential safety signals and fully utilize spontaneous-reporting data; however, such data do not allow the incidence of ADRs to be estimated.

Analysis is based on the disproportion between the number of different ADRs, reported for different drugs. To detect signals pharmacovigilance criteria associated with: proportional reporting ratios (PRRs), Chi Square value (χ^2), number of cases as well as reported odds ratio (ROR) and corresponding lower 95% confidence interval (Lower 95% CI) were used. ROR was calculated as: $(a/c)/(b/d)$ and PRR was calculated as: $[a/(a + b)]/[c/(c + d)]$ - "a" is the number of events of interest reported with the drug of interest, "b" is the number of other events reported with the drug of interest, "c" is the number of events of interest reported with the other drugs, and "d" is the number of other events reported with other drugs. Predefined signal-detection criteria (flags) were applied to identify disproportional reporting patterns and potential safety signals. First flag: PRR identified as 2 or greater ($PRR \geq 2$), second flag: number of reported cases 3 or more ($a \geq 3$), third flag Chi square value at least 4 or greater ($\chi^2 \geq 4$), fourth flag ROR lower 95% CI greater than 1 ($ROR \text{ Lower } 95\% \text{ CI} > 1$) and fifth flag ROR greater than 1 ($ROR \geq 1$). PRRs and RORs were calculated for each drug to evaluate how often the ADRs were reported for a DMT compared to other DMTs, and what were the odds (ROR) of reporting ADR compared to other DMTs. Chi square test and ROR lower 95% CI were used to ensure the statistical significance of the results. When all five predefined criteria were met, the signal was considered positive, indicating that the drug–ADR combination was reported disproportionately more often than the corresponding ADRs associated with the other drugs included in the analysis. Such a signal suggests a potential association but does not establish a strong correlation or causal relationship between the drug and the ADR. Minimal number of cases equal or greater than 3 was utilized to ensure there are no signals based on single reports.

PRR combined with Chi square test as well as ROR combined with its 95% lower CI, presented together with the minimal number of cases are widely used tools for signal detection and data analysis in pharmacovigilance studies, because of the strong statistical properties they possess. ROR is particularly useful when event counts are low, as it handles rare events more robustly than Proportional Reporting Ratio (PRR).

Results

We identified 12,565 reports of ADRs related to neoplasm in all MS DMTs.

The correlation between age and gender of the MS patients treated with the DMT and the neoplastic ADRs proves impossible to be carefully analyzed because of the limitations of the Eudravigilance database. Nevertheless, we identified 9357 reports concerned with female patients, 2488 reports concerned with male patients and 720 reports with missing sex data, marking male to female ratio $\approx 0,27$.

In our analysis five DMTs met the ROR-based criteria only, without fulfilling all five criteria required for a positive signal (see Table 1). These results may suggest that ADRs concerned with neoplasm may occur more often in MS patients treated with those DMTs compared to other studied drugs.

Table 1

The total number of adverse reaction reports and the number of reports of adverse reactions in form of *neoplasm* in multiple sclerosis patients treated with different disease modifying drugs, with PRR, chi-square, RORs, CI. Data presented in descending order of PRR and ROR values, according to the result of the analysis.

Name of the active substance	Year of market approval of the drug (from European Medicines Agency official website)	Follow-up time since	Total number of adverse reaction reports	Neoplasm reported as adverse reaction	Proportional reporting ratio (PRR)	Chi square	Reporting odds ratio (ROR)	ROR 95% Confidence Interval (95%CI)
Mitoxantrone	2002*	2003–2024	597	241	5,55	952,26	8,63	7,29 – 10,20
Fingolimod	2011	2009–2024	18845	1922	1,45	244,58	1,50	1,42 – 1,58
INF beta-1a	1997	2003–2024	36813	3347	1,31	199,15	1,35	1,29 – 1,40
Natalizumab	2006	2006–2024	28274	2524	1,26	117,24	1,29	1,23 – 1,35
Ocrelizumab	2018	2013–2024	10072	802	1,08	5,15	1,09	1,01 – 1,17
Dimethyl-fumarate	2014	2009–2024	23033	1567	0,91	13,35	0,90	0,85 – 0,95
Cladribine	2017 (MS) 2004 (Leukemia)	2004–2024	3754	204	0,73	21,43	0,72	0,62 – 0,83
Siponimod	2020	2015–2024	1192	57	0,65	11,92	0,63	0,47 – 0,82
INF beta-1b	1995	2003–2024	6842	305	0,59	89,50	0,57	0,51 – 0,65
Glatiramer acetate	2001	2003–2024	17923	767	0,55	283,07	0,53	0,49 – 0,57
Alemtuzumab	2013 (MS) 2001 (Leukemia)	2004–2024	4388	165	0,50	86,67	0,48	0,41 – 0,56
Ozanimod	2020 (MS and ulcerative colitis)	2020–2024	909	33	0,49	18,87	0,47	0,32 – 0,67
Teriflunomide	2013	2012–2024	13246	490	0,48	285,77	0,46	0,42 – 0,50
Ofatumumab	2021 (MS) 2010 (Leukemia)	2008–2024	3963	135	0,46	94,04	0,44	0,36 – 0,52
* Mitoxantrone was authorised for MS in several European countries from 2002 through national, not centralised EMA, procedures								

Name of the active substance	Year of market approval of the drug (from European Medicines Agency official website)	Follow-up time since	Total number of adverse reaction reports	Neoplasm reported as adverse reaction	Proportional reporting ratio (PRR)	Chi square	Reporting odds ratio (ROR)	ROR 95% Confidence Interval (95%CI)
Ponesimod	2021	2021–2024	203	6	0,40	5,84	0,38	0,14 – 0,85
* Mitoxantrone was authorised for MS in several European countries from 2002 through national, not centralised EMA, procedures								

The drugs in question were: mitoxantrone with highest ROR equal to 8,63 (95%CI 7,29 – 10,20); fingolimod with ROR = 1,50 (95%CI 1,42 – 1,58); interferon beta 1a with ROR = 1,35 (95%CI 1,29 – 1,40); natalizumab ROR = 1,29 (95%CI 1,23 – 1,35); and finally, ocrelizumab with ROR equal to 1,09 (95%CI 1,01–1,17). ROR-based results may imply further need for close monitoring of those drugs.

Nevertheless, only one of the mentioned drugs produced a strong-enough signal completing all required flags. Mitoxantrone fulfilled both abovementioned ROR as well as PRR criteria PRR = 5,55.

This indicates that neoplasm-related ADRs were reported disproportionately more often for mitoxantrone than for the other DMTs analyzed; being a measure of reporting, it does not by itself establish an increased risk of neoplasm in mitoxantrone-treated patients.

Discussion

Analysis of EudraVigilance on neoplasms reports for MS patients treated with different DMTs available in Europe since 1995 provided essential information on carcinogenesis potential in real-world setting. It is the more important as some of the drugs were suspected of carcinogenetic potential in preregistration or registration period. As examples fingolimod, cladribine and ocrelizumab could be mentioned.[20] What is relevant the real word observation did not confirm all such concerns and in vast majority of cases EudraVigilance analysis did not reveal the risk. This is consistent with the most recent systematic review and meta-analysis of prolonged DMT exposure (13 studies, 333,779 patients with MS, follow-up 6–32 years), which reported a pooled cancer prevalence of 3.8% (95% CI 2.6–5.2) and, in the two studies with an untreated comparator, no significant increase in cancer risk attributable to DMTs (RR 0.8; 95% CI 0.59–1.31). The authors concluded that DMTs alone do not increase cancer risk in patients with MS, although the substantial between-study heterogeneity (I² = 99.7%) and the scarcity of untreated comparators limit this conclusion; our mitoxantrone signal illustrates that risk confined to a single agent may remain undetected in such pooled, class-level estimates.[10]

It is also important to mention that the MS patients treated with DMTs are often under constant and vigilant medical supervision. Many diagnostic procedures are being performed regularly and more often compared to general population. Various diagnostic tools (e.g. magnetic resonance imaging of the brain and spinal cord, chest radiographs etc.) are being used before the initiation of the treatment, as well as, during the treatment. Such an approach might on one hand increase the probability of neoplasm diagnosis in MS patients' cohort, including the period before DMT start and on the other hand, it may lead to a limitation in the use of DMT in patients with contraindications. The sex distribution of the reports, with a male-to-female ratio of approximately 0.27, mirrors the predominance of women among patients treated for MS and might also influence the outcomes of the analysis. Owing to the limitations of the EudraVigilance database, however, neither sex nor age of the reported patients can be related to the size of the corresponding treated populations, which precludes a proper analysis of their role.

Our findings correlate with other available data on neoplastic ADRs in MS patients treated with DMTs. A WHO Pharmacovigilance Database Analysis did show adjusted ROR values above 1 in reported neoplastic ADRs for fingolimod, interferon beta, natalizumab as well as dimethyl fumarate.[21] But, in contrary to WHO database analysis, we did not find an increase in neoplasm in patients treated with dimethyl fumarate. This might, at least partly, be attributed to the difference in analyzed time periods.

The signal-detection criteria applied in the present study were primarily based on the Evan's criteria developed using the UK Yellow Card database [24]. Accordingly, a positive signal required at least three reports of the event of interest ($a \geq 3$), a $PRR \geq 2$ and a chi-square value ≥ 4 . In this analysis Evan's criteria were combined with two ROR-based criteria ($ROR > 1$ and its lower 95% CI > 1), so that a signal was considered positive only when all five criteria were met. A $PRR \geq 2$ indicates that the event accounted for at least twice the proportion of reports for the DMT of interest compared with the reference group.

Except for mitoxantrone none of the abovementioned DMTs produced a strong enough signal. Mitoxantrone, although included in our analysis, currently is not widely used in MS therapy. Its formal approval for MS was first granted by the FDA in the United States in 2000, whereas in Europe the drug was authorised for MS from 2002 onwards through national, not centralised EMA, procedures, and formally approved in France in October 2003 specifically as an induction therapy for highly active relapsing-remitting MS. Because the drug was initially introduced through independent national approvals, the European Medicines Agency (EMA) launched an initiative to standardise its use across all member states. The resulting EU-wide harmonisation restricted its indication to highly active relapsing MS where alternative therapies have failed or are unavailable. Currently, although still accessible it is rarely used in clinical practice due to severe long-term complications, specifically cardiotoxicity and therapy-related acute leukaemia (TRAL). [22] Mitoxantrone, even though, mentioned in the WHO Pharmacovigilance database analysis paper was excluded from the further analysis in the study based on additional indication for treatment of cancer (indication bias).[21] In a French study based on two population-based registries of patients – “European Database for MS”, and the “French National Cancer Register” - mitoxantrone did show elevated relative risk for neoplasm development but the results were deemed statistically non-significant.[23] In a retrospective observational cohort study of 676 patients, with a median follow-up of 8.7 years, 37 patients (5.5%) were diagnosed with a malignancy after mitoxantrone initiation, revealing a standardized incidence ratio of 1.50 (95% confidence interval [CI] 1.05–2.08) based on a comparison to the German general population.[24] French Multiple Sclerosis Society recommends monitoring for therapy-related leukaemia for patients treated with mitoxantrone.[25] The literature on TRAL in mitoxantrone-treated patients with MS is limited to Class III and IV evidence; however, the cumulative incidence appears to be $\approx 0.8\%$. [26, 27]

Even though none other DMT produced a strong enough signal, four of above-mentioned drugs might require further observation based on the ROR value exceeding 1 - suggesting a correlation between the odds of reporting a neoplasm concerned ADR and DMT's use in MS treatment.

The ROR above 1 obtained for interferon beta-1a might suggest an association between the reporting of neoplasms and the use of interferons in the treatment of MS patients. The higher risk of neoplasm was suspected of interferons in the past - especially the probable risk of breast cancer development. However, it was not statistically significant [28] and other available studies disproved that risk for interferons.[23, 29] Two industry-sponsored studies have reported no malignancy risk with IFN- β -1a treatment.[30, 31] Nowadays, due to general decreased use of interferons it might not be possible to definitely assess their potency to trigger carcinogenesis in MS patients.

A WHO Pharmacovigilance Database Analysis suggests a significant association between natalizumab and overall odds of cancer reporting for persons with MS, with ROR value (adjusted to sex, age and geographical region) equal 1.74.[21] In contrary a disproportionality analysis of the Food and Drug Agencies Adverse Event Reporting System Database shows a negative association between odds of reporting a neoplastic ADR characterize as “malignant or unspecific tumor” and natalizumab use with ROR equal to 0.65.[32] Such differences seem hard to explain but might, at least partly be attributed to different definition of neoplastic ADRs taken into account while analyzing both databases, or to difference in the number

of reported ADRs. According to Tysabri Observational Program – long term safety study, during 15 years of observation, low incidence rates (IR) for malignancy were observed (2.8%). The IR for all malignancy types was comparable to that, reported by global cancer observatory - GLOBOCAN, for the general population.[33]

Elevated risk of neoplastic ADRs has also been previously reported in fingolimod treatment. According to summary of product characteristic, higher incidence of lymphomas, as well as, skin cancers including; basal cell carcinoma, cutaneous squamous cell carcinoma, Kaposi's sarcoma, Merkel-cell carcinoma and malignant melanoma has been previously reported.[34] Other available studies on fingolimod and neoplastic ADRs suggest it might indeed elevate the risk of such ADRs. Nationwide registered-based cohort study from Sweden, indicates borderline-significant higher risks of invasive cancer in MS patients treated with fingolimod compared to the general population.[35] Conversely in a Turkish study, based on the official health database maintained by the Ministry of Health of the Republic of Türkiye, fingolimod use was associated with (gender and age-adjusted) odds ratio of cancer slightly lower than one, suggesting that it might not reveal significant changes in cancer risk in treated MS patients.[36, 37]

In case of other than fingolimod S1P modulators such as siponimod, ozanimod and ponesimod, no signal was detected in the present analysis, with ROR values of 0,63, 0,47 and 0,38, respectively. It should be noted there are differences in clinical indications between different S1P modulators. Siponimod is registered for adult patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features of inflammatory activity [38] whereas ozanimod and ponesimod for adult patients with active relapsing remitting multiple sclerosis (RRMS) defined by clinical or imaging features.[39, 40] This difference means that siponimod is generally used in older populations that might be at higher risk of carcinogenesis. Despite this, the present analysis did not show increased reporting of neoplasms for siponimod compared with the other DMTs analysed. S1P receptor modulators (S1PRMs) were previously suspected of carcinogenetic potential. The analysis based on the data from Food and Drug Administration Adverse Event Reporting System (FAERS) indicated that use of S1PRMs might elevate the incidence of skin cancers in treated patients especially basal cell carcinoma in case of siponimod and fingolimod use.[20] This, at least partly, might be attributed to the lymphopenia associated with S1PRMs treatment occurring in MS patients.[41] The differences in the outcomes of above mention analysis and current study might result from difference in time period of data collection (2004–2022 in FARES analysis), as well as, the design of the analysis itself, which was predominantly based only on ROR calculations. FARES database analysis was also concerned with skin cancers only.. The present analysis did not show increased reporting of neoplasms for siponimod compared with the other DMTs.

Available up-to date data does not show any connection between ocrelizumab and neoplasm development. According to summary of product characteristics and available studies the previously suspected risk of neoplasm development, during ocrelizumab treatment, was not observed. In a safety analyses based on integrated clinical and laboratory data, calculated standardized incidence ratios (SIRs) indicate no significant excess in the incidence of all malignancies in the ocrelizumab all-exposure population compared with a typical MS population or the general population. The SIR for breast cancer indicates no increased risk in women treated with ocrelizumab compared with a typical MS population and a nonsignificant excess compared with the general US population.[42] The adjusted RORs calculated for ocrelizumab in the WHO Pharmacovigilance Database Analysis were equal to 0,93.[21] Moreover, both the ROR and the PRR calculated for ocrelizumab in this analysis barely exceeded 1 and the PRR did not reach the predefined threshold of 2, indicating that the odds of reporting a neoplasm-related ADR were only marginally higher than for the other DMTs used in MS treatment.

Strengths and limitations of the study

The main strength of the study is utilization of the pan-European ADR database, collecting all DMTs safety data coming from different populations and countries. It plays an essential role in understanding safety profile in the real-world condition. Such approach allows detection of rarely occurring or unexpected adverse events when the drug goes widely to the patients' populations. It enables regulatory agencies promptly respond to emerging safety concerns. On the other hand,

disproportionality analysis identifies correlations but not causation and it cannot establish definitive cause-effect relationship. Moreover, based on spontaneous reporting it is not possible to take into account all factors responsible for oncogenesis for individual patients, including confounding factors such as genetic status, underlying health conditions, lifestyle factors or the effect of changing therapies within the time of disease duration. Underreporting typical for spontaneous reporting system is crucial and well known limitation. Moreover, it is not possible to precisely define number of patients that receive each therapy and we provide only the general number of cancer cases reported in the database. One should also remember that longer time of use of the drug may also stand for higher probability of reporting oncologic ADR at least due to increasing patients' age.

Despite many limitations which must be considered, databases such as Eudravigilance remain significant sources of pharmacovigilance data, providing crucial safety information and are valuable for post-marketing safety monitoring. The healthcare professionals should be aware of their irreplaceable role in the system.

Conclusions

Available scientific data, as well as, the results of this real-world data analysis, suggest that most DMTs used in MS, with the exception of mitoxantrone, are not associated with disproportionately increased reporting of neoplasms in treated patients. Drugs modulating disease progression, including HETA, do not appear to increase the reporting of cancer and other malignancies. Other risk factors such as age should be taken into account and the use of DMTs should be still carefully monitored. Remaining uncertainties might be disproven in the future, when more data collected within the longer period of time is available for careful analysis. Submission of ADR reports persists as an irreplaceable tool in pharmacovigilance, enabling medical professionals to provide the safest available treatment for the patients.

Abbreviations

ADR	adverse drug reaction
CI	confidence interval
CNS	central nervous system
DMT	disease modifying therapy
FAERS	Food and Drug Administration Adverse Event Reporting System
HETA	high-efficacy therapy
IR	incidence rate
LOMS	late onset multiple sclerosis
MS	multiple sclerosis
PRR	proportional reporting ratio
ROR	reporting odds ratio
RRMS	

relapsing remitting multiple sclerosis
SIR
standardized incidence ratio
S1PRMs
S1P receptor modulators
SPMS
secondary progressive multiple sclerosis

Declarations

Author contributions

Rafał Kułakowski: *conception and design, acquisition of data, preparing the primary version of materials and methods, data statistical analysis, interpretation of the results, drafting the manuscript, revising the manuscript critically for important intellectual content*

Michał Chrzanowski: *conception and design, acquisition of data*

Iwona Rościszewska-Żukowska: *conception and design, preparing the primary version of introduction, revising the manuscript critically for important intellectual content, final approval*

Maciej Niewada: *conception and design, acquisition of data, data statistical analysis, interpretation of the results, revising the manuscript critically for important intellectual content*

Dagmara Mirowska-Guzel: *conception and design, acquisition of data, interpretation of the data, preparing the primary version of discussion, revising the manuscript critically for important intellectual content, final approval*

Founding statement

No additional founding was acquired for this study. Authors have no other financial holdings or considerations that could possibly influence the objectivity of this report.

Data availability

The data that support the results of the study are openly available in EudraVigilance at <https://www.adrreports.eu/>.

Ethical approval

Not applicable

Conflict of interest statement

Rafał Kułakowski: no conflict of interest

Michał Chrzanowski: employed at pharmaceutical company AstraZeneca in a position that is not related to commercial activities; employer does not conduct any activities pertaining to the development or promotion of medicinal products used in the treatment of multiple sclerosis.

Iwona Rościszewska-Żukowska: no conflict of interest

Maciej Niewada: co-founder of HealthQuest, a consultancy firm providing services in the area of reimbursement of medical technologies; received honoraria for lectures and participation in expert advisory meetings from various pharmaceutical

companies, both national and international, including Boehringer Ingelheim, Merck, MSD, Polpharma, Adamed, Ipsen, Thea, Simon-Kucher, and others operating in the healthcare sector.

Dagmara Mirowska-Guzel: received compensation for lectures and consulting services from Biogen, Novartis, Neuraxpharm, Roche, Merck, Teva, BMS, GSK, Bayer, Sandoz and Sanofi-Genzyme. None of the consulting agreements are relevant to the submitted work.

Disclosure of using artificial intelligence (AI) in the writing process

No AI or AI-assisted technologies were used in the preparation of this manuscript.

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