Acta Neurologica Scandinavica

WILEY

RESEARCH ARTICLE OPEN ACCESS

Replicating Safety Signals for Natalizumab Treatment in Multiple Sclerosis Patients Using German Administrative Health Insurance Claims Data

Alicia Başoğlu[1] | Mona Reifferscheid[2] | Christine M. Marx[2,3] | Maike Below[2] | Ellen Kexel[4] | Alexander Stahmann[5] | Ursula Drechsel-Bäuerle[6] | Brigitte Keller-Stanislawski[6] | Klaus Berger[1]

[1]Institute of Epidemiology and Social Medicine, University of Münster, Münster, Germany | [2]Central Research Institute of Ambulatory Health Care in the Federal Republic of Germany, Berlin, Germany | [3]Medical Advisory Service Berlin Brandenburg, Berlin, Germany | [4]Department of Care Management, BKK Dachverband e.V, Berlin, Germany | [5]German Multiple Sclerosis Register, MS Forschungs-und Projektentwicklungs-gGmbH, Hannover, Germany | [6]Paul-Ehrlich-Institute, Langen, Germany

Correspondence: Alicia Başoğlu (alicia.basoglu@uni-muenster.de)

Received: 19 December 2025 | **Revised:** 2 June 2026 | **Accepted:** 24 June 2026

Academic Editor: Suraiya Saleem

Keywords: adverse events | claims data | multiple sclerosis | natalizumab | safety signal | spontaneous reporting system | statutory health insurance

ABSTRACT

Introduction: Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system. Immunotherapies such as natalizumab are associated with rare, serious adverse events that were identified by the spontaneous reporting system.

Objective: To replicate safety signals from the spontaneous reporting system for natalizumab treatment in MS patients using two data sources (ds) of German statutory health insurance (SHI) data.

Methods: We analyzed administrative SHI claims data from 44 company medical funds (ds1, 2010–2018) and 12 German physicians' associations (ds2, 2013–2018). Patients with a validated MS diagnosis (ICD-10-GM G35) treated with natalizumab until either subsequent other immunotherapies (natalizumab-switcher) or no other following immunotherapy (natalizumab-non-switcher) were included. We searched for safety signals, based on a list of signals derived from the EMA spontaneous reporting system, and calculated odds ratios (ORs) for incident diseases using interferon therapy as a comparison.

Results: Overall, 36,798 MS patients were included. Although case numbers were low for most investigated diseases, a safety signal of progressive multifocal leukoencephalopathy (PML) could be replicated for natalizumab-switcher (ds1: OR = 28.88 [6.02, 138.50]; ds2: OR = 59.94 [28.43, 147.32]) and natalizumab-non-switcher (ds1: OR = 28.74 [5.82, 141.88]; ds2: OR = 34.33 [15.43, 87.43]). For natalizumab-switcher, furthermore, a safety signal for herpes simplex was reproduced (ds1: OR = 1.84 [1.27, 2.68]; ds2: OR = 1.48 [1.24, 1.77]). In ds2, increased risks were observed also for herpes zoster (natalizumab-switcher: OR = 1.74 [1.49, 2.03]; natalizumab-non-switcher: OR = 1.36 [1.17, 1.58]) and "other polyneuropathies" (natalizumab-switcher: OR = 1.42 [1.17, 1.70]).

Conclusions: Replication of safety signals for specific medications using German administrative SHI data is possible but requires very large datasets to obtain a sufficiently large study sample that allows the identification of rare adverse events such as PML.

1 | Introduction

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease that affects approximately 2.8 million people worldwide, and women are about two times more likely to have a diagnosis compared to men [1]. The number of effective disease-modifying treatments (DMTs) has increased during the last few decades. One of these DMTs is the monoclonal antibody natalizumab, a recombinant humanized anti-α4-integrin antibody produced in a murine cell line by recombinant DNA technology [2]. The pharmaceutical effect of natalizumab is a selective immunosuppression. It is directed towards a specific antigenic target, the alfa4 integrin on the surface of lymphocytes, so that lymphocytes are unable to enter the brain and attack myelin protein. After cases of progressive multifocal leukoencephalopathy (PML), a serious viral infection of the brain, were reported, natalizumab was temporarily withdrawn from the market [3]. The first two cases occurred in the phase III study SENTINEL after 29 and 37 doses of natalizumab [4]. Since then, more than 900 confirmed cases have been documented during the postmarketing phase, primarily in Europe, with an incidence of 34.8 per 10,000 patients treated with natalizumab (as of August 1, 2023) [5]. To increase patients' safety, use of natalizumab was restricted to second-line therapy by the European Medicines Agency (EMA). Furthermore, annual MRI for safety monitoring was mandatory, and all patients who were treated with natalizumab for over 2 years had to be informed about the risks in detail [6].

Due to the restricted number of study participants, the short follow-up, and the narrow inclusion criteria, detection of rare adverse drug reactions (ADRs) in clinical trials is limited [7]. Thus, data from spontaneous reporting systems, for example, of the European ADR database (EudraVigilance), are important for pharmacovigilance and for early detection of signals of new, rare, or serious ADRs in the population actually treated after drug approval [8, 9]. Spontaneous reporting systems have the advantage of covering the entire patient population. However, accurate quantification of risks is limited because the applied denominator information on drug utilization can be imprecise, and the numerator can be biased by underreporting [9].

In contrast, German administrative statutory health insurance (SHI) claims data include denominator information on prescribed drugs in large populations. Moreover, for accounting and billing reasons, the numerator of ADRs in the form of diagnoses requiring medical treatment is likely to be reported more completely by health care providers. Especially, hospital admissions after drug prescriptions can serve as information about possible serious ADRs [10]. In Germany, nearly 90% of the total population is insured with a SHI fund because health insurance is compulsory by legislation and health care services are broadly covered by SHI. Hence, administrative SHI claims data are an appropriate basis to comprehensively describe healthcare in Germany in a population-based approach. Daily practice including off-label use of drugs can be assessed, and exposure and outcome are documented independently, which prevents reporting bias [11]. Due to their size, longitudinal coverage, and timeliness, these data can be well utilized for investigating ADRs in drug safety research [10]. Therefore, our aim was to reproduce safety signals from the spontaneous reporting system by analyzing two data sources with German administrative SHI claims data.

2 | Materials and Methods

This analysis was conducted within a study on the applicability of different data sources for improving the pharmacovigilance of innovative therapies using the example of MS (project VerSI-MS-PV).

2.1 | Data sources

We used two different sources of administrative SHI data for the replication of safety signals (Table 1). For data source 1 (ds1), the association of company medical funds (BKK Dachverband e.V.) collected billing data from 44 member funds covering 7.6 million people. Data on inpatient and outpatient care, as well as drug prescriptions from the years 2010–2018, were provided. Data source 2 (ds2) was provided by the Central Research Institute of Ambulatory Health Care in the Federal Republic of Germany (Zi) and included data on outpatient care and drug prescriptions from the years 2013 to 2018. These data were available for 12 of the 17 regional Associations of Statutory Health Insurance Physicians that cover 65.6 million people, which is 90% of those insured by the statutory health system. Therefore, ds2 was considerably larger than ds1, and the datasets were partially overlapping (about 15%), but there was no linkage between them. Data on outpatient care of ds1 should be represented also in ds2 but not

TABLE 1 | Data time periods of patient selection, drug exposure, and follow-up for the two data sources.

Year	2010	2011	2012	2013	2014	2015	2016	2017	2018
Data source 1	Index diagnosis of MS[a]								
				Drug exposure and follow-up					
Data source 2	—[b]	—	—	Index diagnosis of MS[a]					
	—	—	—		Drug exposure and follow-up				

Abbreviation: MS, multiple sclerosis.
[a]Selection of patients with a prevalent multiple sclerosis diagnosis.
[b]Data were not available for these years.

the data on inpatient care. The datasets were not pooled, and the results were not aggregated.

In both data sources, demographic information, outpatient diagnoses according to ICD-10-GM (German Modification of the International Classification of Diseases, 10th Revision), outpatient medication (Anatomical Therapeutic Chemical [ATC] codes; DDD, defined daily dose), and outpatient billing codes (EBM, German uniform assessment standard) were available. Furthermore, ds1 contained inpatient diagnoses as well as operations and procedures in hospitals (OPS, German Procedure Classification). In ds2, valid information on death was not available. Outpatient diagnoses were classified by an indicator regarding the diagnostic certainty. The categories were "certain," "excluded," or "suspected," and if patients had a prior history of the disease, the diagnosis was classified as "status post."

2.2 | Patient population and study design

We included patients with a documented MS diagnosis (ICD-10-GM G35) within the first year of the respective observation time. Patients were allowed to enter the study population only once; multiple entries were not permitted. Outpatient diagnoses with a diagnostic certainty classified as "certain" were considered in both datasets. In ds1, also inpatient principal and treatment diagnoses were taken into account. Documented diagnoses had to be validated by a following MS diagnosis within 3 subsequent calendar quarters. This validation is called the M2Q criterion, which translates to "at least two quarters." We excluded minors younger than 18 years, patients with an unclear year of birth, and patients who were pregnant during the observation time.

In this analysis, we focused on patients who were treated with natalizumab, either with no other subsequent DMT (denoted as "natalizumab-non-switcher") or with a following change in medical therapy ("natalizumab-switcher"). We compared them to patients who were treated exclusively with interferons during the observation period ("interferon-non-switcher"). For this categorization, interferon beta-1a, interferon beta-1b, and peginterferon beta-1a were subsumed. We chose interferon-non-switcher as a comparison since it is an established treatment option. Patients treated exclusively with DMTs other than natalizumab and interferons were excluded from our analysis. A therapy-free interval prior to the examined treatment was not required because natalizumab is not a first-line therapy for de novo patients with MS, but rather an escalation therapy for patients with unfavorable prognostic factors and a persistent disease activity with relapse and lesions under basic therapy [5]. An escalation of therapy from, for example, glatiramer acetate, fingolimod, or dimethyl fumarate to natalizumab was usually considered when the immunosuppressive effect of the previous medication was insufficient. Therefore, a washout period to allow the previous medication to fully metabolize and clear from the body before starting natalizumab therapy would not be envisaged. However, the reasons for therapy-free intervals between two treatments are not coded in the health insurance claims data.

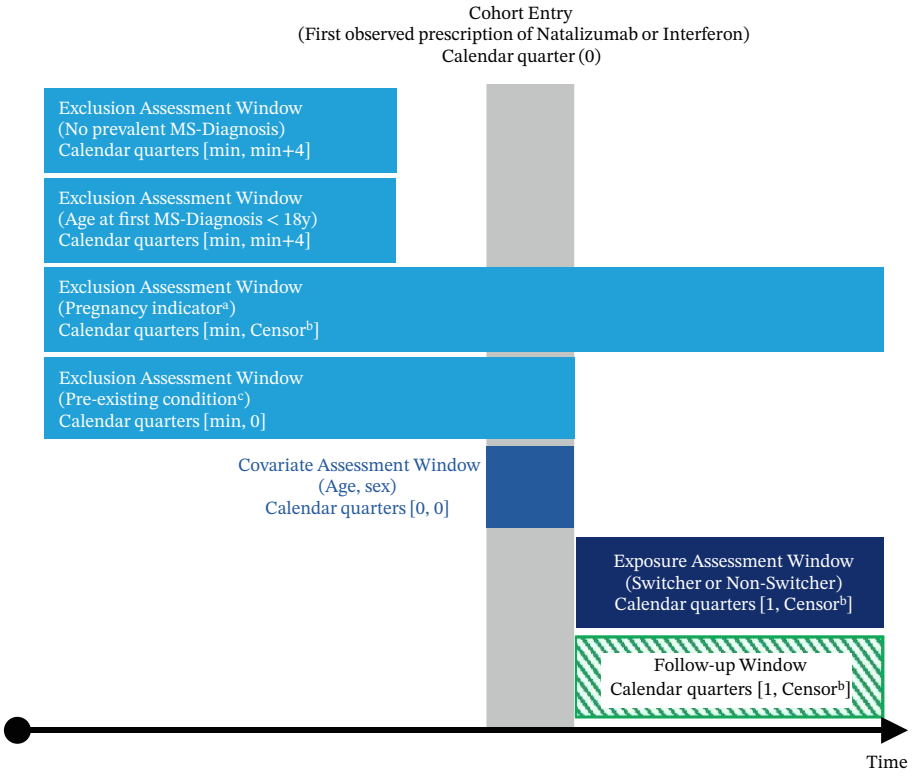
The cohort entry of the patients was the calendar quarter of the first observed prescription of natalizumab (for natalizumab-switcher and natalizumab-non-switcher) or interferon (for interferon-non-switcher) (Figure 1). We assessed the first year of the patient-specific observation time to exclude patients without a "validated," prevalent MS diagnosis and patients younger than 18 years. The exclusion assessment window for pregnancy indicators encompassed the overall observation period. Preexisting conditions were determined in the calendar quarter of the cohort entry and in the whole observation time prior to that. Exposure to other subsequent DMTs after natalizumab was assessed in the observation period after cohort entry for categorization into natalizumab-switcher or natalizumab-non-switcher. Follow-up began in the calendar quarter after the quarter of cohort entry and was censored on December 31, 2018, or at the time of changing the health insurance company or at the time of death.

2.3 | Safety Signals From the Spontaneous Reporting System

We searched on the website of the EMA for outcomes of confirmed safety signals regarding natalizumab from the years 2013 to 2018. The signals had been detected in the "EudraVigilance" database of the EMA or other scientific and regulatory sources, and have been evaluated and published by the Pharmacovigilance Risk Assessment Committee (PRAC). Furthermore, we searched in a database of the German Federal Institute for Vaccines and Biomedicines (Paul-Ehrlich-Institut). Figure 2 summarizes the signal management process within the European Union and shows the context of safety signals that are designated as "confirmed." We selected such confirmed safety signals and assigned ICD-10-GM codes to the diseases reported in the notification (Table S1: "Selected safety signals and ICD-10-GM codes" on page 1 of the electronic supporting information). Documented diagnoses of the following 10 diseases were analyzed: disseminated chorioretinitis (H30.1), affections of the eye (H59.9), folic acid deficiency anemia (D52.9), acquired isolated aplastic anemia (D60), other aplastic anemias, pancytopenia (D61.18), PML (A81.2), herpes simplex (B00), herpes zoster (B02), polyneuritis (G61), and other polyneuropathies (G62).

2.4 | Outcome and Statistical Analysis

To describe the characteristics of the patient population, we assessed the proportion of females, median age, and median duration of treatment during the observation period. We calculated odds ratios (ORs) for each of the listed incident diseases, considering outpatient diagnoses classified as "certain" as well as inpatient principal and treatment diagnoses. As only incident diagnoses were assessed, we excluded patients from the respective analysis who had the disease within the first quarter of the drug treatment or prior to that. Thus, the denominator of patients at risk varied between the examined outcomes. The individual look-back periods for the identification of previous diseases start with the beginning of the period under observation and end in the first quarter of the respective drug treatment. Therefore, the length of the look-back periods differs between patients. Incident diseases were not only considered if they were diagnosed under treatment, but also if diseases occurred after the end of the therapy or after a treatment



a. Patients with a pregnancy indicator during the observation period were excluded.
b. Observation time ended on December 31st, 2018, or at the time of changing the health insurance company, or at the time of death.
c. Patients with a diagnosis of the investigated disease within the first quarter of the drug treatment or prior to that were excluded.

FIGURE 1 | Study design.

switch. For patients assigned to the "natalizumab-switcher" group according to their treatment regimen in the observation period after cohort entry, diseases occurring before the switch were still taken into account for the "natalizumab-switcher" group. ORs were adjusted for age and sex, and we report 95% Wald confidence intervals and p values with $\alpha = 0.05$. The two data sources were analyzed separately to examine the robustness of the results. Due to data security reasons, case numbers under 10 are not shown for ds2.

For MS patients who developed PML after the first quarter of their drug treatment, we calculated the duration of medication until the first documented PML diagnosis according to the prescribed DDD. As we included patients with a prevalent MS diagnosis in the first year under observation, the time windows during which an individual is considered exposed could potentially be left censored. We additionally assessed the proportions of deceased PML patients, of cases with an inpatient diagnosis of PML, and of cases with a PML onset under treatment. Furthermore, we described the most frequent sequences of DMT stratified by natalizumab-switcher and natalizumab-non-switcher based on ds1. The investigators, A.B., M.R., and C.M., performed the analyses and had full access to the dataset of the insured MS patients to apply the inclusion criteria for creating the study population. Analyses were carried out using SAS 9.4 (SAS Institute Inc., Cary, NC) and R (Version 4.3.1).

3 | Results

3.1 | Patient Population

Ds1 comprised administrative SHI data of 40,760 patients insured at company medical funds, who had an outpatient diagnosis of MS (ICD-10-GM G35) with a diagnostic certainty classified as "certain" or an inpatient principal or treatment diagnosis during the period 2010–2018 (Figure 3). The diagnosis was validated according to the M2Q criterion for 36,459 patients, and 21,353 of them had a diagnosis in the first year under observation. As data were provided only for adults, almost all patients ($n = 21,244$) were aged 18 years or older at their first MS diagnosis in the observation period. More than half of the patients had a DMT prescription ($n = 11,413$), and most of them ($n = 10,417$) neither had outpatient billing codes that indicated a pregnancy during the observation period nor such inpatient operations or procedures. The final study population includes 4221 patients with natalizumab or interferon treatment, which is 10.4% of the initial 40,760 MS patients. They were treated either with natalizumab and subsequently with other DMT (natalizumab-switcher: $n = 607$) or with natalizumab and no other following DMT (natalizumab-non-switcher: $n = 548$) or exclusively with interferon during the whole observation period (interferon-non-switcher: $n = 3066$).

The ds2 of the regional Associations of Statutory Health Insurance Physicians was more than 7-fold larger and contained data of

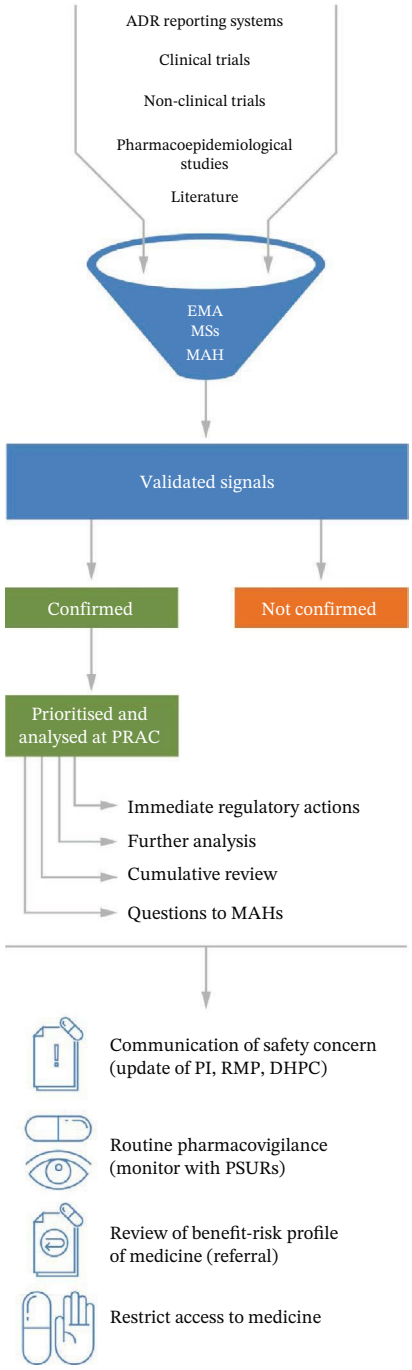


FIGURE 2 | Summary of the signal management process within the European Union and consequent recommendations of PRAC. ADR, adverse drug reaction; DHPC, direct healthcare professional communication; EMA, European Medicines Agency; MAH, marketing authorisation holder; MSs, member states; PI, product information; PRAC, Pharmacovigilance Risk Assessment Committee; PSUR, Periodic Safety Update Report; RMP, risk management plan. (cited from Potts J, Genov G, Segec A, Raine J, Straus S, Arlett P. Improving the Safety of Medicines in the European Union: From Signals to Action. Clin Pharmacol Ther. March 2020; 107(3): 521–9.) [12].

300,837 patients with a "certain" outpatient MS diagnosis in the years 2013–2018 (Figure 4). Compared to ds1, a slightly smaller proportion of patients had a diagnosis that fulfilled the M2Q criterion (ds1: 89.4%; ds2: 84.3%, $n = 253,684$), and 177,733 patients had a prevalent diagnosis in the first year under observation. Similar to ds1, almost all patients ($n = 172,072$) were 18 years of age or older, more than half of them were treated with DMT ($n = 89,056$), and most of them ($n = 83,076$) had no outpatient billing code indicating a pregnancy. Finally, 10.8% of the initial 300,837 MS patients were included ($n = 32,577$) and categorized as natalizumab-switcher ($n = 3,629$), natalizumab-non-switcher ($n = 4602$), and interferon-non-switcher ($n = 24,346$).

The proportion of women was lower in ds1 compared to ds2 in all three treatment groups (interferon-non-switcher: 67.3% vs. 70.5%, natalizumab-switcher: 61.9% vs. 71.3%, natalizumab-non-switcher: 66.4% vs. 73.2%), and the patients were slightly younger (Table 2). The median duration of treatment, however, was similar in both data sources. natalizumab-non-switcher had a longer duration of treatment than Switcher (ds1: 3.12 years; ds2: 3.37 years vs. ds1: 1.97 years; ds2: 1.48 years). The mean observation time after cohort entry was similar for natalizumab-switcher (6.1 years) and the comparison group interferon-non-switcher (6.2 years) (ds1; data not shown). However, natalizumab-non-switcher had less time available (4.1 years) and hence a lower probability of the outcome to occur. In ds1, DMT treatment before natalizumab included most frequently interferon and glatiramer acetate for both natalizumab-switcher and natalizumab-non-switcher (Table S2).

3.2 | Replication of Safety Signals

Although the datasets were very large, case numbers were low for most of the assessed "signal" diseases or even zero in some subgroups, for example, for "acquired isolated aplastic anemia"; "other aplastic anemias, pancytopenia"; or "disseminated chorioretinitis" (Table 3). In both data sources, the safety signal of PML was clearly replicated by sex and age adjusted OR for natalizumab-switcher (ds1: OR = 28.88 [6.02, 138.50]; ds2: OR = 59.94 [28.43, 147.32]) as well as for natalizumab-non-switcher (ds1: OR = 28.74 [5.82, 141.88]; ds2: OR = 34.33 [15.43, 87.43]) (Figure 5 and Table 3). Furthermore, an increased risk was observed for herpes simplex in natalizumab-switcher (ds1: OR = 1.79 [1.22, 2.62]; ds2: OR = 1.48 [1.24, 1.77]). The safety signal for herpes zoster was affirmed in ds2 for both patient groups (natalizumab-switcher: OR = 1.74 [1.49, 2.03]; natalizumab-non-switcher: OR = 1.36 [1.17, 1.58]). Moreover, a risk for "other polyneuropathies" was identifiable in ds2 for natalizumab-switcher (OR = 1.42 [1.17, 1.70]). Estimates calculated in the much larger ds2 had a better precision with smaller confidence intervals. Risks tend to be higher for natalizumab-switcher than for natalizumab-non-switcher, but the confidence intervals of these subgroups were generally overlapping.

3.3 | MS Patients With PML

The number of patients with an incident PML diagnosis was $n = 9$ (ds1) and $n = 56$ (ds2) in natalizumab-switcher as well as $n = 8$ (ds1) and $n = 35$ (ds2) in natalizumab-non-switcher (Table 4). In ds1, one natalizumab-switcher with PML and two affected natalizumab-non-switcher died within the observation period. Not only an outpatient diagnosis but also a hospital diagnosis of ICD-10-GM A81.2 were documented for

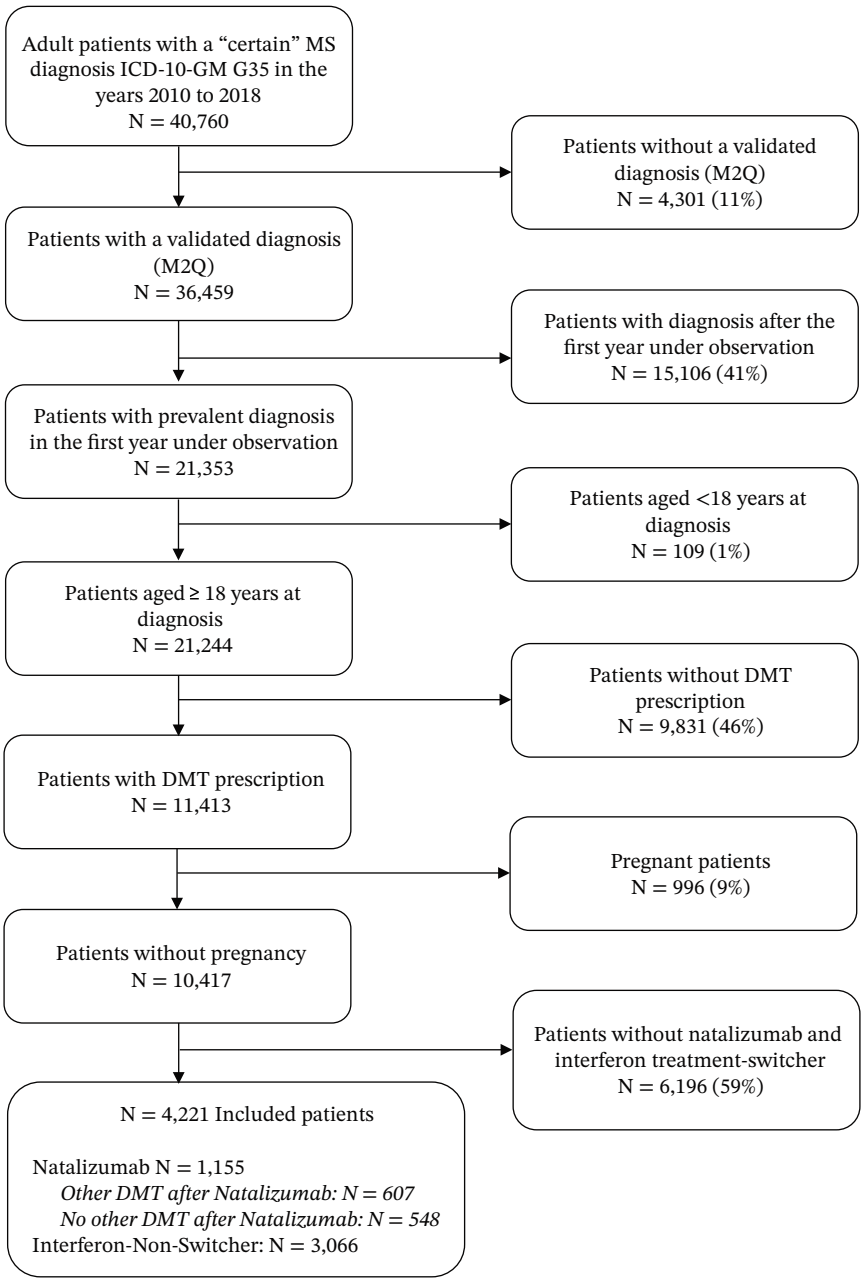


FIGURE 3 | Study flowchart for data source 1. DMT, disease-modifying treatment; M2Q, validation criterion; MS, multiple sclerosis.

all nine PML cases in natalizumab-switcher and for seven of the eight cases in natalizumab-non-switcher (ds1). All three deceased PML cases had an inpatient diagnosis. Seven of the 19 PML cases in ds1 had an inpatient PML diagnosis but no outpatient diagnosis (interferon-non-switcher $n = 1$; natalizumab-switcher $n = 4$; natalizumab-non-switcher $n = 2$). Preexisting conditions of PML cases in ds1 were unspecified diabetes mellitus (ICD-10 E14; $n = 1$) and spondylosis (ICD-10 M47; $n = 2$) in the group of natalizumab-non-switcher. Median duration of medication with natalizumab until the first diagnosis of PML was longer in natalizumab-non-switcher (ds1: 2.4 years and ds2: 2.1 years) compared to natalizumab-switcher (ds1: 2.2 years and ds2: 1.6 years). The deceased PML cases were treated with natalizumab for a longer period of time (ds1; natalizumab-switcher: 4.4 years and natalizumab-non-switcher: 3.2 years). In about one-quarter of cases, the first PML diagnosis was documented in a calendar quarter with a natalizumab prescription.

4 | Discussion

We assessed the usability of two different sources of administrative SHI claims data to complement the signal management process illustrated in Figure 2. To reproduce "confirmed" safety signals from the spontaneous reporting system for natalizumab treatment, sex and age-adjusted ORs of corresponding incident diseases were calculated based on the overall 36,798 included MS patients in two data sources with German administrative SHI claims data. Despite low case numbers for most of the assessed diseases, we found several PML diagnoses and calculated OR between 28.7 and 59.9 in the assessed patient groups. Hence, this

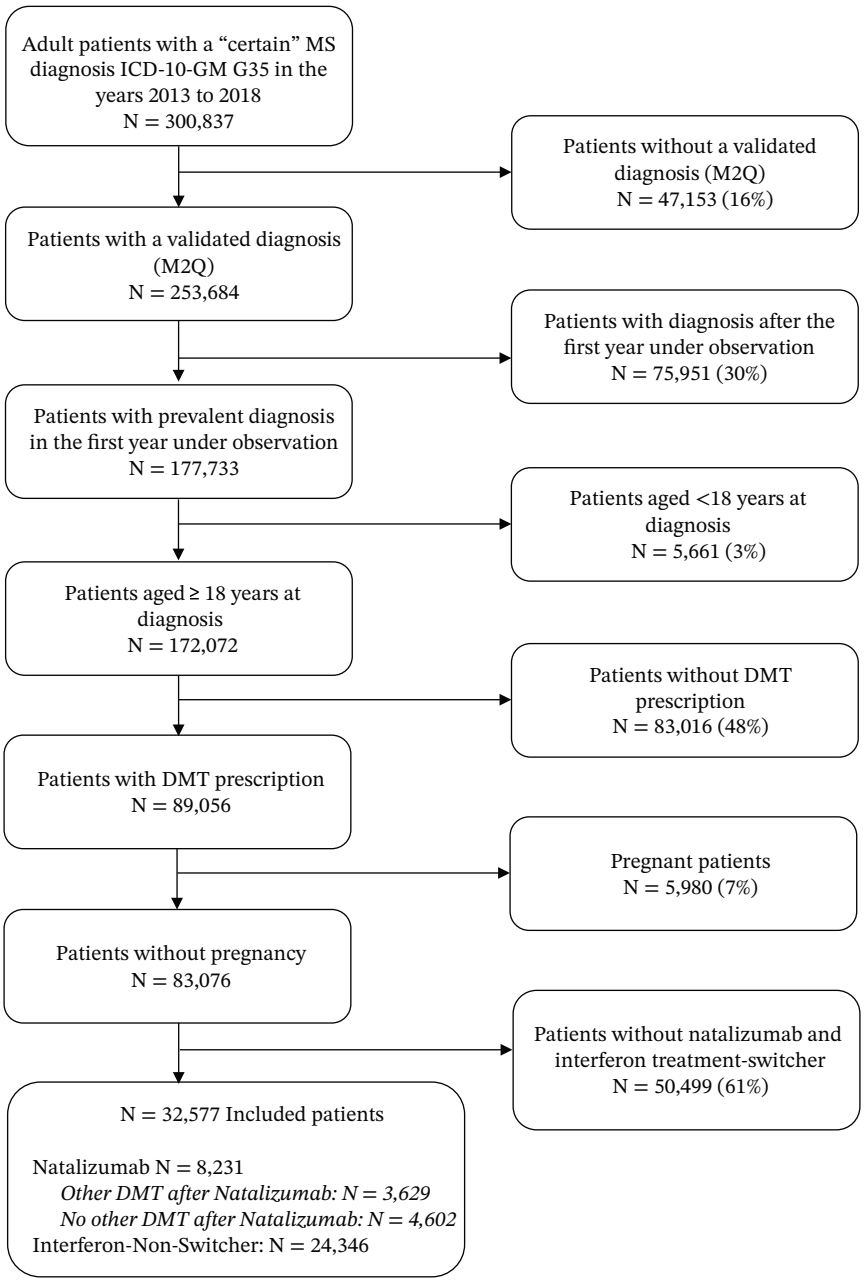


FIGURE 4 | Study flowchart for data source 2. DMT, disease-modifying treatment; M2Q, validation criterion; MS, multiple sclerosis.

TABLE 2 | Characteristics of included MS patients.

Treatment	*N*	Sex (% female)	Age (median)	Duration of treatment[a] (median, years)
Interferon-non-switcher (ds1)	3066	67.3	44	4.49
Natalizumab-switcher (ds1)	607	61.9	38	1.97
Natalizumab-non-switcher (ds1)	548	66.4	36	3.12
Interferon-non-switcher (ds2)	24,346	70.5	47	4.63
Natalizumab-switcher (ds2)	3629	71.3	39	1.48
Natalizumab-non-switcher (ds2)	4602	73.2	38	3.37

Abbreviations: ds1, data source 1; ds2, data source 2.
[a]According to the prescribed DDD for natalizumab or interferon, respectively.

TABLE 3 | Risks of specific incident diseases in MS patients treated with natalizumab who had the respective disease after the first quarter of the drug treatment or later for treatment switcher and non-switcher in the two data sources.

Disease	Nata. *N*	*n*	Interf. *N*	*n*	OR[a]	95 CI		*p* value
A812 Progressive multifocal leukoencephalopathy								
Switcher (ds1)	605	9	3065	2	28.88	6.02	138.50	< 0.001
Non-switcher (ds1)	548	8	3065	2	28.74	5.82	141.88	< 0.001
Switcher (ds2)	3623	56	24,339	< 10[b]	59.94	28.43	147.32	< 0.001
Non-switcher (ds2)	4601	35	24,339	< 10	34.33	15.43	87.43	< 0.001
B00 Herpes simplex								
Switcher (ds1)	597	39	3044	120	1.79	1.22	2.62	0.001
Non-switcher (ds1)	533	21	3044	120	1.03	0.64	1.68	0.852
Switcher (ds2)	3577	169	24,174	766	1.48	1.24	1.77	< 0.001
Non-switcher (ds2)	4512	149	24,174	766	1.02	0.84	1.23	0.846
B02 Herpes zoster								
Switcher (ds1)	591	40	3047	195	1.24	0.87	1.78	0.238
Non-switcher (ds1)	533	24	3047	195	0.83	0.53	1.29	0.403
Switcher (ds2)	3582	235	24,186	1099	1.74	1.49	2.03	< 0.001
Non-switcher (ds2)	4496	232	24,186	1099	1.36	1.17	1.58	< 0.001
D529 Folic acid deficiency anemia								
Switcher (ds1)	606	3	3066	4	5.023	1.04	24.27	0.044
Non-switcher (ds1)	546	1	3066	4	1.87	0.19	18.00	0.588
Switcher (ds2)	3628	12	24,328	54	1.97	0.98	3.66	0.043
Non-switcher (ds2)	4591	14	24,328	54	1.81	0.93	3.28	0.064
D60 Acquired isolated aplastic anemia								
Switcher (ds1)	607	0	3066	0	—	—	—	—
Non-switcher (ds1)	548	0	3066	0	—	—	—	—
Switcher (ds2)	3629	0	24,346	< 10	—	—	—	—
Non-switcher (ds2)	4601	< 10	24,346	< 10	10.32	0.35	314.68	0.131
D61.18 Other aplastic anemias, pancytopenia								
Switcher (ds1)	607	0	3066	0	—	—	—	—
Non-switcher (ds1)	548	0	3066	0	—	—	—	—
Switcher (ds2)	3629	0	24,346	0	—	—	—	—
Non-switcher (ds2)	4602	0	24,346	0	—	—	—	—
G61 Polyneuritis								
Switcher (ds1)	605	1	3059	3	3.30	0.29	37.44	0.336
Non-switcher (ds1)	546	0	3059	3	—	—	—	—
Switcher (ds2)	3623	< 10	24,304	32	1.96	0.77	4.38	0.122
Non-switcher (ds2)	4594	< 10	24,304	32	0.47	0.08	1.63	0.315
G62 Other polyneuropathies								
Switcher (ds1)	592	22	2990	139	1.15	0.72	1.85	0.558

(Continues)

TABLE 3 | (CONTINUED)

Disease	Nata. *N*	*n*	Interf. *N*	*n*	OR[a]	95 CI		*p* value
Non-switcher (ds1)	528	11	2990	139	0.68	0.36	1.28	0.234
Switcher (ds2)	3534	145	23,672	968	1.42	1.17	1.70	< 0.001
Non-switcher (ds2)	4464	145	23,672	968	1.19	0.98	1.42	0.071
H301 Disseminated chorioretinitis								
Switcher (ds1)	607	1	3065	0	—	—	—	—
Non-switcher (ds1)	547	0	3065	0	—	—	—	—
Switcher (ds2)	3629	< 10	24,343	12	1.31	0.29	4.37	0.683
Non-switcher (ds2)	4597	< 10	24,343	12	0.32	0.02	1.71	0.279
H599 Affections of the eye								
Switcher (ds1)	606	1	3066	4	2.02	0.20	19.95	0.548
Non-switcher (ds1)	547	0	3066	4	—	—	—	—
Switcher (ds2)	3627	< 10	24,334	47	0.92	0.27	2.34	0.878
Non-switcher (ds2)	4600	< 10	24,334	47	0.76	0.23	1.95	0.614

Abbreviations: ds1, data source 1; ds2, data source 2.
[a]Adjusted for sex and age.
[b]For data source 2 case numbers under 10 are not shown due to data security reasons but the risks are reported.

safety signal was replicated in both data sources for natalizumab-switcher as well as for natalizumab-non-switcher. Increased risks were furthermore observed for herpes simplex, herpes zoster, and "other polyneuropathies," at least in one of the data sources or patient groups. Natalizumab-switcher had slightly higher risks than natalizumab-non-switcher. The latter had a longer duration of medication with natalizumab during the study period under observation until their first diagnosis of PML. The same was seen for PML cases, who died within the study period.

According to the summary of product characteristics for natalizumab, it is unknown if patients have an increased risk of PML, who were switching from DMTs with an immunosuppressant effect to this treatment [2]. Hence, more frequent monitoring is recommended for these patients. In our analysis, DMTs with an immunosuppressant effect administered prior to natalizumab were not taken into consideration for the categorization of patient groups. Instead, we differentiated between patients with a change in DMT treatment after natalizumab and with no other subsequent DMT. In both data sources, we found a longer duration of treatment for natalizumab-non-switcher than for switcher. This also applied to PML cases until their first diagnosis of PML. However, the OR for PML was higher in natalizumab-switcher than in natalizumab-non-switcher, at least in ds2.

The observed increased risks for herpes simplex and herpes zoster are in line with clinical trials that found herpes infections slightly more frequently in natalizumab-treated patients than in a placebo group. After natalizumab treatment with a duration of a few months to several years in the postmarketing setting, cases of encephalitis and meningitis were reported, which were serious, life-threatening, and sometimes fatal [2]. In some cases, the encephalitis and meningitis were associated with acute retinal necrosis [5]. In clinical trials, adverse reactions such as headache, nasopharyngitis, fatigue, urinary tract infection, nausea, arthralgia, and dizziness occurred with natalizumab administration [2]. Additionally, hematological changes and an increase in liver enzymes due to hepatoxicity or the development of autoimmune hepatitis were observed [13]. A systematic review of the safety and efficacy of monoclonal antibodies for patients with the subtype progressive MS showed that the most commonly reported adverse events associated with natalizumab in that patient group were urinary tract infection, nasopharyngitis, and falls [14].

4.1 | Strengths and Limitations

The large population-based data sources, which are not affected by recall bias, are a major strength of this study. The low case numbers of the rare incident diseases we observed, especially in ds1, emphasize that many SHI must be included for replicating or identifying safety signals in administrative claims data. Validity of outpatient diagnoses was increased by considering only recordings with a diagnostic certainty classified as "certain" that fulfilled the M2Q criterion. Robustness of the results was assessed by analyzing the two data sources separately, which reinforced the identified risk for PML. On the one hand, ds1 comprised inpatient and outpatient claims data whereby incident diseases could be identified in both settings; on the other hand, ds2 included only outpatient data but was much larger and represented insured patients from various kinds of SHI. The latter moreover strengthens the generalizability (external validity) of the results for the German population.

A general limitation of administrative claims data used in drug safety research is that they were primarily collected for billing of healthcare services and not for research purposes. Thus, only a small amount of clinical data (e.g., diagnoses, medication, and procedures) is documented, and confounders

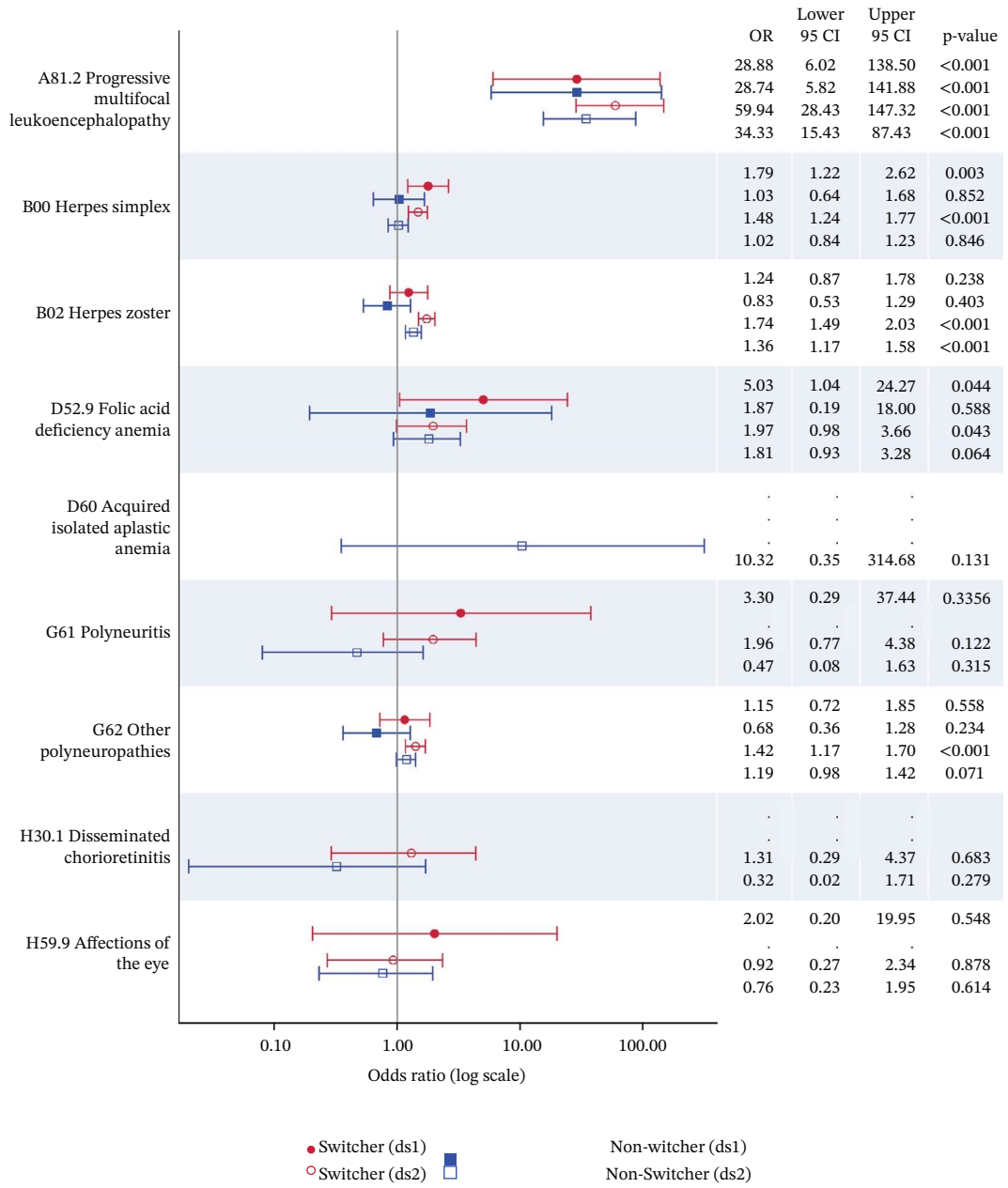


FIGURE 5 | Odds ratios (adjusted for sex and age) of specific incident diseases in MS patients treated with natalizumab who had the respective disease after the first quarter of the drug treatment or later, presented separately for treatment switcher and non-switcher in the two data sources (ds1 and ds2).

related to lifestyle, for example, smoking, alcohol consumption, or diet, were not available. Another aspect was that a large proportion of MS patients were treated with different DMTs over time, which made it difficult to attribute the onset of slowly developing diseases to a specific DMT. Therefore, we stratified our analysis into natalizumab-switcher and natalizumab-non-switcher. However, as data availability on the medication history is limited (left truncation of the drug exposure), the extent of a possible misclassification cannot be specified. Prior DMTs before initiation of natalizumab treatment could have had long-term effects on the occurrence of the assessed diseases. The stratification into the groups natalizumab-switcher and natalizumab-non-switcher addresses also a possible selection bias due to healthy adherers or sick stoppers of a therapy. Natalizumab-switcher possibly changed DMT because of an ADR, and therefore, stratified analyses were performed. Furthermore, disease severity and degree of disability are not documented in SHI claims data and could differ between the patient groups. Additionally, the number of deceased cases of PML could not be reported for ds2. Both data sources included information on DMT administered in the outpatient setting, but no data on medication during hospital stays. However, natalizumab infusions are usually administered in outpatient care, and therefore, the database adequately captures the drug exposure. The temporal relationship between DMT prescription and the occurrence of the safety signal was not taken into account. Natalizumab-non-switcher had a lower mean observation time than

TABLE 4 | Duration of medication of MS patients who developed PML, inpatient diagnosis, and PML onset under treatment for the two data sources.

	All cases of PML		Deceased cases of PML	
N (ds1)				
Interferon-non-switcher (ds1)	2		0	(0%)
Natalizumab-switcher (ds1)	9		1	(11%)
Natalizumab-non-switcher (ds1)	8		2	(25%)
N (ds2)				
Interferon-non-switcher (ds2)	< 10[a]		—[b]	
Natalizumab-switcher (ds2)	56		—	
Natalizumab-non-switcher (ds2)	35		—	
Cases with inpatient diagnosis of PML				
Interferon-non-switcher (ds1)	1	(50%)	—	
Natalizumab-switcher (ds1)	9	(100%)	1	(100%)
Natalizumab-non-switcher (ds1)	7	(88%)	2	(100%)
Interferon-non-switcher (ds2)	—[c]		—	
Natalizumab-switcher (ds2)	—		—	
Natalizumab-non-switcher (ds2)	—		—	
Duration of respective medication[d] (median, years)				
Interferon-non-switcher (ds1)	2.80		—	
Natalizumab-switcher (ds1)	2.22		4.36	
Natalizumab-non-switcher (ds1)	2.42		3.21	
Interferon-non-switcher (ds2)	0.54		—	
Natalizumab-switcher (ds2)	1.64		—	
Natalizumab-non-switcher (ds2)	2.06		—	
PML onset under respective treatment[e]				
Interferon-non-switcher (ds1)	0	(0%)	0	(0%)
Natalizumab-switcher (ds1)	2	(22%)	0	(0%)
Natalizumab-non-switcher (ds1)	1	(13%)	0	(0%)
Interferon-non-switcher (ds2)	< 10	(29%)	—	
Natalizumab-switcher (ds2)	15	(27%)	—	
Natalizumab-non-switcher (ds2)	11	(31%)	—	

Abbreviations: ds1, data source 1; ds2, data source 2; PML, progressive multifocal leukoencephalopathy.

[a]Case numbers under 10 are not shown for data source 2 due to data security reasons.

[b]No valid information on death available in data source 2.

[c]Data source 2 covers only outpatient care.

[d]Medication with interferon or natalizumab according to prescribed DDD until the first diagnosis of PML.

[e]In the same calendar quarter as interferon or natalizumab prescription.

natalizumab-switcher (4.1 vs. 6.1 years). This alone can already result in lower ORs. However, the confidence intervals of the two stratified natalizumab groups were generally overlapping. Another issue to consider is the time passed since the observation period (2010/2013–2018). In recent years, there has been a paradigm shift in MS treatment. Induction therapy, that is, the primary use of highly active substances as the standard of care for all affected MS patients in early stages of the disease ("hit hard and early"), has been increasingly discussed [5]. Moreover, the current dosing of natalizumab might be different due to the option to increase intervals between doses to reduce the risk of developing adverse events.

Furthermore, the mapping of safety signals using the ICD classification is limited. For example, ICD category G62, which is assigned to granule cell neuronopathy, also includes other forms of polyneuropathy, such as alcohol-induced polyneuropathy. Other potential causes of the investigated safety signals were not accounted for through specific exclusion criteria. For instance, ocular changes coded under H59.9 can occur postoperatively as a consequence of surgery. Moreover, access to German SHI data is complicated due to severe restrictions by the Code of Social Law (Section 75, Book 10) and administrative rules in the application process. This limits the use of SHI data, and thus, a reform of these rules is necessary [15].

5 | Conclusions

Safety signals for the risk of PML, herpes simplex, herpes zoster, and "other polyneuropathies" in MS patients treated with

natalizumab were replicated using two large datasets. However, for some rare incident diseases, risk estimates could not be calculated due to low case numbers, which underlines the necessity of very large databases. German administrative SHI claims are a useful data source to complement the spontaneous reporting system, not only in the therapeutic area of MS but also for other indications, especially those with many newly authorized immunotherapies.

Author Contributions

All coauthors contributed to the study conception and design. Alicia Başoğlu, Mona Reifferscheid, and Christine M Marx performed the data analysis. The first draft of the manuscript was written by Alicia Başoğlu. All coauthors commented on previous versions of the manuscript.

Acknowledgments

We acknowledge support from the Open Access Publication Fund of the University of Münster.

Funding

German Health Care Innovation Fund, 01VSF18038. Open Access funding enabled and organized by Projekt DEAL.

Disclosure

All authors read and approved the final manuscript. The results of this study were presented by Alicia Basoglu at the annual conference of the German Society for Epidemiology (DGEpi) in Würzburg, Germany, on September 28, 2023, and at the German Congress for Health Services Research (DKVF) in Berlin, Germany, on October 6, 2023. Furthermore, the results were presented by Christine Marx at the Annual Conference of the Society for Drug Use Research and Drug Epidemiology (GAA) in Köln, Germany, on November 9, 2023, and at the Brandenburg Congress for Health Services Research in Rüdersdorf, Germany, on November 16, 2023.

Ethics Statement

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the Medical Association Westphalia-Lippe and the University of Münster (project code: 2019-362-f-S).

Consent

We analyzed preexisting claims data, originally collected as part of routine administrative processes by statutory health insurance providers. Permission to use the data for scientific research was granted in accordance with legal requirements, and consent to participate was not necessary for this study.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

For data protection law reasons, no data are available. All analytic code used for the analysis is available from Alicia Başoğlu and Mona Reifferscheid on reasonable request. The manuscript follows the guidance from the reporting of studies conducted using observational routinely collected health data statement for pharmacoepidemiology (RECORD-PE) statement.

References

1. C. Walton, R. King, L. Rechtman, et al., "Rising Prevalence of Multiple Sclerosis Worldwide: Insights From the Atlas of MS, third edition," *Multiple Sclerosis* 26, no. 14 (2020): 1816–1821, https://doi.org/10.1177/1352458520970841.

2. European Medicines Agency, "Natalizumab (Tysabri)," (2018), https://www.ema.europa.eu/en/medicines/human/EPAR/tysabri.

3. M. Gonzalez-Lorenzo, B. Ridley, S. Minozzi, et al., "Immunomodulators and Immunosuppressants for Relapsing-Remitting Multiple Sclerosis: A Network Meta-Analysis," *Cochrane Database of Systematic Reviews* 1, no. 1 (2024): CD011381, https://doi.org/10.1002/14651858.CD011381.pub3.

4. R. A. Rudick, W. H. Stuart, P. A. Calabresi, et al., "Natalizumab Plus Interferon Beta-1a for Relapsing Multiple Sclerosis," *New England Journal of Medicine* 354, no. 9 (2006): 911–923, https://doi.org/10.1056/NEJMoa044396.

5. A. Berthele, and K. Gehring, "Guideline on Diagnosis and Treatment of Multiple Sclerosis [Diagnose und Therapie der Multiplen Sklerose, Neuromyelitis-Optica-Spektrum-Erkrankung (NMOSD) und MOG-IgG-Assoziierten Erkrankung (MOGAD)]," *DGNeurologie* 4, no. 4 (2021): , https://doi.org/10.1007/s42451-021-00334-6.

6. P. S. Sørensen, "Balancing the Benefits and Risks of Disease-Modifying Therapy in Patients With Multiple Sclerosis," *Journal of the Neurological Sciences* 311 (2011): S29–S34, https://doi.org/10.1016/S0022-510X(11)70006-5.

7. I. Pigeot, and W. Ahrens, "Databases as a Source for Monitoring Systems of Drug Safety," *Die Monatszeitschrift Bundesgesundheitsblatt – Gesundheitsforschung – Gesundheitsschutz* 47, no. 6 (2004): 513–517, https://doi.org/10.1007/s00103-004-0834-3.

8. X. F. Jiao, L. Pu, S. Lan, et al., "Adverse Drug Reaction Signal Detection Methods in Spontaneous Reporting System: A Systematic Review," *Pharmacoepidemiology and Drug Safety* 33, no. 3 (2024): e5768, https://doi.org/10.1002/pds.5768.

9. L. Hazell, and S. A. W. Shakir, "Under-Reporting of Adverse Drug Reactions," *Drug Safety* 29, no. 5 (2006): 385–396, https://doi.org/10.2165/00002018-200629050-00003.

10. R. Foraita, L. Dijkstra, F. Falkenberg, et al., "Aufdeckung von Arzneimittelrisiken Nach der Zulassung," *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* 61, no. 9 (2018): 1075–1081, https://doi.org/10.1007/s00103-018-2786-z.

11. I. Pigeot, and W. Ahrens, "Establishment of a Pharmacoepidemiological Database in Germany: Methodological Potential, Scientific Value and Practical Limitations," *Pharmacoepidemiology and Drug Safety* 17, no. 3 (2008): 215–223, https://doi.org/10.1002/pds.1545.

12. J. Potts, G. Genov, A. Segec, J. Raine, S. Straus, and P. Arlett, "Improving the Safety of Medicines in the European Union: From Signals to Action," *Clinical Pharmacology & Therapeutics* 107, no. 3 (2020): 521–529, https://doi.org/10.1002/cpt.1678.

13. L. Moiola, P. S. Rommer, and U. K. Zettl, "Prevention and Management of Adverse Effects of Disease Modifying Treatments in Multiple Sclerosis," *Current Opinion in Neurology* 33, no. 3 (2020): 286–294, https://doi.org/10.1097/WCO.0000000000000824.

14. Z. Sabahi, A. Daei Sorkhabi, A. Sarkesh, A. Naseri, N. Asghar-Rezaei, and M. Talebi, "A Systematic Review of the Safety and Efficacy of Monoclonal Antibodies for Progressive Multiple Sclerosis," *International Immunopharmacology* 120 (2023): 110266, https://doi.org/10.1016/j.intimp.2023.110266.

15. E. Garbe, and I. Pigeot, "Der Nutzen Großer Gesundheitsdatenbanken Für Die Arzneimittelrisikoforschung," *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* 58, no. 8 (2015): 829–837, https://doi.org/10.1007/s00103-015-2185-7.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Supporting Information.** Table S1: Selected safety signals and ICD-10-GM codes. Table S1 shows the confirmed safety signals that were selected and the corresponding ICD-10-GM codes that were assigned to the diseases reported in the signal notification. Table S2: Most frequent sequences of disease-modifying treatments (DMTs) in data source 1 for natalizumab-switcher and natalizumab-non-switcher. Table S2 outlines the DMTs before natalizumab for natalizumab-switcher and natalizumab-non-switcher in data source 1.