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SYSTEMATIC REVIEW

Drug-Induced Progressive Multifocal Leukoencephalopathy (PML): A Systematic Review and Meta-Analysis

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Abstract

Introduction Progressive multifocal leukoencephalopathy (PML) was first described among patients affected by hematological or solid tumors. Following the human immunodeficiency virus (HIV) epidemic, people living with HIV have represented most cases for more than a decade. With the diffusion of highly active antiretroviral therapy, this group progressively decreased in favor of patients undergoing treatment with targeted therapy/immunomodulators. In this systematic review and meta-analysis, the objective was to assess which drugs are most frequently related to PML development, and report the incidence of drug-induced PML through a meta-analytic approach.

Methods The electronic databases MEDLINE, EMBASE, ClinicalTrials.gov, Web of Science and the Canadian Agency for Drugs and Technologies in Health Database (CADTH) were searched up to May 10, 2022. Articles that reported the risk of PML development after treatment with immunomodulatory drugs, including patients of both sexes under the age of 80 years, affected by any pathology except HIV, primary immunodeficiencies or malignancies, were included in the review. The incidence of drug-induced PML was calculated based on PML cases and total number of patients observed per 100 persons and the observation time. Random-effect metanalyses were conducted for each drug reporting pooled incidence with 95% confidence intervals (CI) and median (interquartile range [IQR]) of the observation time. Heterogeneity was measured by I^2 statistics. Publication bias was examined through funnel plots and Egger's test.

Results A total of 103 studies were included in the systematic review. In our analysis, we found no includible study reporting cases of PML during the course of treatment with ocrelizumab, vedolizumab, abrilumab, ontamalimab, teriflunomide, daclizumab, inebilizumab, basiliximab, tacrolimus, belimumab, infliximab, firategrast, disulone, azathioprine or danazole. Dalfampridine, glatiramer acetate, dimethyl fumarate and fingolimod show a relatively safe profile, although some cases of PML have been reported. The meta-analysis showed an incidence of PML cases among patients undergoing rituximab treatment for multiple sclerosis (MS) of 0.01 cases/100 persons (95% CI − 0.08 to 0.09; $I^2 = 20.4\%$; $p = 0.25$) for a median observation period of 23.5 months (IQR 22.1–42.1). Treatment of MS with natalizumab carried a PML risk of 0.33 cases/100 persons (95% CI 0.29–0.37; $I^2 = 50\%$; $p = 0.003$) for a median observation period of 44.1 months (IQR 28.4–60) and a mean number of doses of 36.3 (standard deviation [SD] ± 20.7). When comparing data about patients treated with standard interval dosing (SID) and extended interval dosing (EID), the latter appears to carry a smaller risk of PML, that is, 0.08 cases/100 persons (95% CI 0.0–0.15) for EID versus 0.3 cases/100 persons (95% CI 0.25–0.34) for SID.

Conclusions A higher risk of drug-related PML in patients whose immune system is not additionally depressed by means of neoplasms, HIV or concomitant medications is found in the neurological field. This risk is higher in MS treatment, and specifically during long-term natalizumab therapy. While this drug is still routinely prescribed in this field, considering the efficacy in reducing MS relapses, in other areas it could play a smaller role, and be gradually replaced by other safer and more recently approved agents.

Extended author information available on the last page of the article

Key Points

Natalizumab appears to be correlated to a risk of 0.33 cases/100 persons (95% CI 0.29–0.37) for a median observation period of 44.1 months (IQR 28.4–60) and a mean number of doses of 36.3 (SD ± 20.7). Extended interval dosing carries a lower risk of PML, that is, 0.08 cases/100 persons (95% CI 0.0–0.15) for EID versus 0.3 cases/100 persons (95% CI 0.25–0.34) for SID.

We found a risk of PML after rituximab administration of 0.01 cases/100 persons for a median observation period of 23.5 months (IQR 22.1–42.1), noting the included population is only a part of patients undergoing treatment with this drug.

In our analysis, we found no includible study reporting cases of PML during the course of treatmentwith ocrelizumab, vedolizumab, abrilumab, ontamalimab, teriflunomide, daclizumab, inebilizumab, basiliximab, tacrolimus, belimumab, infliximab, firategrast, disulone, azathioprine or danazole.

1 Introduction

Human polyomavirus 2 (HPyV-2), previously known as JC Polyomavirus (JCPyV or JCV), is a member of the Polyomaviridae family, genus *Polyomavirus*, isolated for the first time in 1971 in a patient affected by Hodgkin's lymphoma who died of progressive multifocal leukoencephalopathy (PML), a potentially fatal disease of the central nervous system (CNS) [1, 2]. The viral genome is composed of a 5.13Kb supercoiled circular enclosed double-stranded DNA, containing three regions known as the early coding region, the late coding region and the non-coding control region (NCCR). The early region encodes the alternatively spliced transforming proteins, large tumor antigen (T-Ag) and small tumor antigen (t-Ag), both involved in viral replication. The late region encodes for capsid proteins VP1, VP2 and VP3 and a small regulatory protein, known as agnoprotein, apparently involved in the trafficking of capsid proteins to the nucleus [3, 4].

Early and late coding regions are separated by the NCCR, a genetic sequence essential for viral replication. This sequence can be found in two different forms: a non-rearranged, non-pathogenic form (i.e. archetype form) most frequently found in the urine of healthy subjects, and a rearranged more virulent form (i.e. prototype form) typically detected in the cerebrospinal fluid, brain and blood of PML patients.

The neurotropic pathogenic form is characterized by duplications of the promoter/enhancer elements and deletions of the suppressor elements, these being rearrangements associated with PML development [5, 6].

The virus affects only the human species and has a strong tropism for glial cells, kidney epithelial cells and B lymphocytes. Primary infection takes place by unclear mechanisms; nevertheless, 50–90% of the adult population (range depending on the age and country referred to) presents anti-JCPyV antibodies, suggesting a probable tendency of the virus to cause asymptomatic infections during childhood [5].

JCPyV enters target cells via the serotoninergic 5HT-2a receptor and by binding an N-linked glycoprotein with a terminal α(2,6)-linked sialic acid, both present in a wide variety of human cells. Once JCPyV has entered the cells, a latent infection is established in both kidneys and the lymphoid system. Upon immunosuppression, the virus undergoes a replicative cycle, gaining access to the blood and overcoming the blood–brain barrier [7].

Neurotropic mutants preferably target the oligodendrocytes, where replication provokes an accumulation of viral particles, nuclear enlargement, neuronal apoptosis, and in turn, multifocal demyelination [5].

Although no consensus exists on the various clinical subtypes of PML, Cortese and colleagues referred to specific phenotypes of the disease as 'classical PML', 'inflammatory PML' or 'PML IRIS' [2]. The classical form can involve supratentorial and infratentorial structures, with neurological symptoms depending on the location involved, most commonly represented by cognitive and behavioral abnormalities, sensory and motor deficits, seizures, ataxia, and aphasia. Inflammation-related symptoms and signs could be absent. Conversely, the inflammatory form is usually an expression of an immune reconstitution inflammatory syndrome (IRIS). In some cases, the uncontrolled associated inflammatory response can be fatal during the acute phase. Other pathological manifestations of JCPyV include granule cell neuronopathy, fulminant encephalopathy and JCPyV meningitis [2].

After an initial rise in PML cases described in patients affected by hematological or solid tumors, a second rise was observed during the AIDS pandemic in the 1980s, when people living with human immunodeficiency virus (HIV) represented the vast majority (50–80%) of cases. During the next decades, thanks to the introduction and diffusion of highly active antiretroviral therapy, this patient group progressively decreased in favor of patients affected by autoimmune or neoplastic diseases, or in those undergoing treatment with targeted therapy/immunosuppressants [1, 7]. In the literature, drug-induced PML is most notably correlated with use of natalizumab, a monoclonal antibody acting on α-4 integrin, but a growing amount of data is now available for other immunosuppressants and biologic drugs. To

date, multiple sclerosis patients undergoing immunosuppressant treatment represent a large proportion of drug-induced PML cases, but several other drugs have been investigated as possibly correlated to PML and/or mention PML as a risk in their prescription information. Examples include alemtuzumab, brentuximab vedotin, dimethyl fumarate, efalizumab, fingolimod, ibrutinib, obinutuzumab, ocrelizumab, ofatumumab, glatiramer acetate, dalfampridine and rituximab [8, 9].

In this systematic review and meta-analysis, the authors aimed to summarize and assess which drugs are most frequently associated with PML development [8], and report the incidence of drug-induced PML through a meta-analytic approach.

2 Methods

This systematic review and meta-analysis is reported according to the Preferred Reporting Items for Systematic Reviews and meta-Analyses (PRISMA) statement [10]. Details of the protocol for this systematic review were registered on PROSPERO (CRD42022332587).

2.1 Research Question

This systematic review was aimed at answering the question: what is the incidence of drug-induced PML in patients under the age of 80 years, affected by pathologies requiring immunosuppressant treatment, but not affected by HIV, primary immunodeficiencies or malignancies? The question was structured according to the PICOS statement as follows:

Population: people of both sex under the age of 80 years, affected by any pathology but HIV, primary immunodeficiencies or malignancies.

Intervention: exposure to immunosuppressants as indicated for the treatment of their baseline pathologies, regardless the specifics of the latter. Only exposure to drugs known to carry some degree of risk for PML development was considered.

Comparison: the risk of PML was assessed for each drug independently and compared with that of the untreated affected population.

Outcome: estimating the risk of PML development after treatment with each included drug.

Study design: only observational studies and randomized controlled trials (RCTs) were considered eligible for selection.

2.2 Search Strategy and Study Selection

Eligible studies were identified via searching on the following electronic databases: MEDLINE, EMBASE, ClinicalTrials.gov, Web of Science and the Canadian Agency for Drugs and Technologies in Health Database (CADTH).

An initial search was performed on all existing literature up to May 10, 2022, without restrictions in terms of language or publication period. Fully published and peer-reviewed studies were identified by MEDLINE, EMBASE, ClinicalTrials.gov and Web of Science database search, while unpublished studies were sought via the CADTH and selected according to the inclusion criteria. The specific search strategy as elaborated for each mentioned database is available as electronic supplementary material (ESM; S1). After database searching, all results were merged on the online tool Rayyan in order to be deduplicated and selected according to their relevance and the inclusion/exclusion criteria [11]. LVR, RI, DK, NB, IF, FDM, VB and BM all participated to the selection process, which was held, for each record, in blind by at least three authors. Discrepancies in selection were resolved by discussion or by VM, LS or the project coordinator, MI.

As for relevance and eligibility, a first round of elimination was performed in blind by reading the study abstract and title only. Then, a second round of selection was performed by reading the study full text. All phases were supervised by VM and LS.

A detailed flowchart of the selection process is shown in Fig. 1.

2.3 Inclusion and Exclusion Criteria

The inclusion process was limited to RCTs, cohort studies and cross-sectional studies describing or reporting the use of drugs correlated to the development of PML and controlling for PML events over time after administration. Case reports, case series, reviews, or any other study design were considered ineligible. Included populations were any subject up to 80 years of age, who received treatment for at least 3 months with one or more drugs correlated to the development of PML, regardless the pathology requiring such treatment. Subjects older than 80 years of age were excluded, as age itself could represent a factor altering the immune system predisposing to the development of PML [12, 13]. In order to focus the attention on drug-induced cases of PML, people living with HIV, hematological/oncological patients or patients affected by primary immunodeficiencies were considered not eligible for inclusion. Furthermore, we excluded studies reporting administration of mixed or unclear drug regimens, in order to limit possible misinterpretations of the results.

2.4 Data Extraction

Abstracted information was extracted by LVR, RI, DK, NB, IF, FDM, VB and BM, and was entered into a computerized

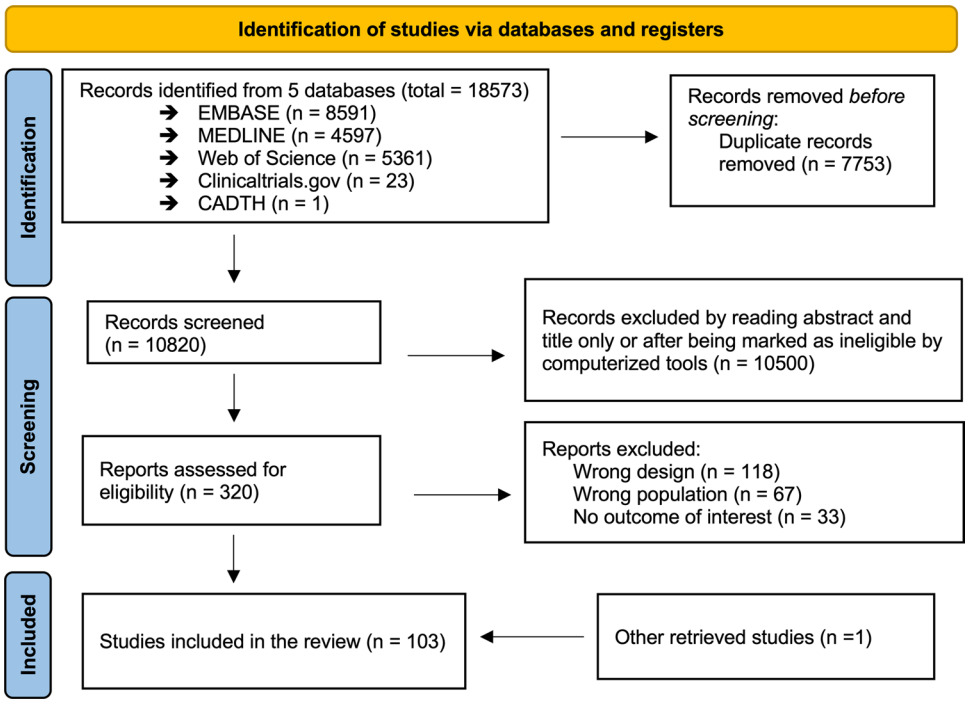

Fig. 1 PRISMA flowchart—Selection process of included studies

master log. Extracted information included journal, year of publication, first author name, title of the publication, country, study design, study period in months, sample size, sample demographic characteristics, baseline pathology, trial registration number (if applicable), drug name and posology, number of patients developing PML at any time during treatment (number of events), timing of PML development (timing of events), median treatment duration in months, number of drug infusions (median of the cohort), standard/extended interval dosing (for natalizumab only), data about placebo group if present, follow-up period, patient-years and percentage of the population positive to antibodies against JCPyV. Additional data were also gathered for PML cases, such as previous immune-suppressant treatment, number of drug infusions (median), timing of development of PML, treatment strategy for PML cases, information about immune reconstitution syndrome if reported, outcome of PML cases and PML cases in patients undergoing modifications of their treatment regimen. Study investigators were contacted for unreported data or additional details, when needed. Extracted data was checked and elaborated for the meta-analysis by DZ.

2.5 Meta-Analysis

By means of a meta-analytic approach, authors tried to provide a rapid view of the risk of drug-induced PML in patients whose immune system is not additionally depressed by means of neoplasms, HIV or concomitant medications. This was done by analyzing the risk of PML development as reported in the included studies, taking into account drug regimens, exposed population, drug exposure time and relative infusion protocols (e.g. standard interval dosing vs extended interval dosing for natalizumab; different rituximab infusion protocols for its various indications). We excluded from our analysis those studies with promiscuous or unclear drug regimens, such as drug regimens involving two or more drugs both known to carry a risk of PML. This was done to reduce the risk of misinterpreting the results. When median (interquartile range, IQR) of treatment duration was given, we calculated mean and standard deviation (SD) in order to be able to include the studies in the same meta-analysis [14, 15]. Also, when not reported, in order to compare extended interval dosing and standard interval dosing we calculated the mean number of doses based on the treatment duration and dose interval.

The incidence of drug-induced PML was calculated for each drug potentially correlated to PML based on the number of PML cases and total number of patients observed per 100 persons and the observation time as reported in each study. Subsequently, random-effect meta-analyses were conducted for each drug reporting pooled incidence with 95% confidence intervals (CI) and the mean (SD) or median (IQR) of the observation time of all the studies included in the meta-analyses. Forest plots were used for the graphical representation of each meta-analysis.

Heterogeneity was measured by I^2 statistic, considering it important when > 50% [16].

Subgroup analysis was also performed for different natalizumab infusion protocols (i.e. standard interval dosing and

extended interval dosing) in order to highlight the possible differences in terms of risk of PML development. Publication bias was examined graphically through funnel plots and Egger's test, where $p < 0.05$ indicates significant publication bias [17].

The meta-analysis was performed on Stata v.15.0 software (Stata Corp, College Station, TX, USA).

2.6 Quality Appraisal of Included Studies

Each included study was assessed by means of the Cochrane risk of bias tool 2 (RoB2) for clinical trials, or by the Newcastle-Ottawa scale (NOS) for observational studies [18, 19]. Observational studies were divided into very high, high, and low risk of bias, with high risk of bias being assigned to studies scoring between 4 and 6 points on the NOS [19].

The assessment of the risk of bias was performed in blind by IF, VB, BM, DK, FDM and RAC. Disagreements between reviewers was resolved by discussion or by contacting VM, LS or the lead reviewer, MI.

3 Results

3.1 Bibliographic Search

An initial database search on the above-mentioned databases collectively identified 18,573 studies. After merging all records on the computerized tool Rayyan, 7753 duplicates were identified, and, after manual confirmation, removed. After screening the remaining records by title and abstract, 320 were eligible for further assessment by analyzing the full article text. After application of the inclusion and exclusion criteria, 103 studies were selected for the systematic review (Fig. 1).

3.2 Study Characteristics and Included Population

Included studies were published between 2005 and 2022. This review included 76 observational studies [9, 18, 20–94], 26 RCTs [95–120], and data from a pharmacovigilance database [121].

Thirty-two were multicenter studies (31.06%); 15 were based in Italy (14.56%); 11 in the USA (10.67%); 8 in France (7.76%); Germany and Spain contributed with 6 studies each (5.82%); Netherlands contributed with 5 studies (4.85%); Japan with 4 studies (3.88%); and Sweden, Portugal, Switzerland and the UK with 2 studies each (1.94%). Austria, Brazil, Greece, Hungary, Israel, Kuwait, Lebanon and Norway contributed with one study each (0.97%).

Sample sizes of included studies ranged from 9 to 100,921 patients for a total of 228,817 patients.

The mean included population age was 45.51 years (± 12.54). When data about gender was available, male gender represented approximately 27.54% of the included population.

Data about the pathologies discussed in the included studies is depicted in order of frequency in Table 1.

Populations in included studies were most frequently undergoing treatment with natalizumab ($n = 65$), rituximab ($n = 21$), fingolimod ($n = 10$), interferon ($n = 14$), ocrelizumab ($n = 4$), vedolizumab ($n = 4$) and dimethyl fumarate ($n = 4$). Complete information about all treatment regimens is available in Tables 2 and 3. Given the great number of included studies, the heterogeneity of pathologies and drug regimens, accordingly to our primary objective, and not least, for the sake of maintaining clarity in our manuscript, we decided to focus our discussion on those studies describing at least one case of PML; however, full information about all studies is available in Tables 2 and 3.

3.3 Quality Assessment

All included observational studies were evaluated using the NOS and divided into classes of risk as previously described in the methods section. Two studies were rated as having a very high risk of bias (0–3 NOS points), 59 were rated as having a high risk of bias (4–6) and the remaining studies were rated as having a low risk of bias (7–9). As for the 26 included randomized studies evaluated using the RoB2 tool, 10 were evaluated to have a high risk of bias, 11 showed some concern and five were rated to have a low risk of bias. A detailed chart reporting each subdomain for both the RoB2 tool and the NOS is available in the ESM (S2, S3), while a synthetic view of these data is also available above in Tables 2 and 3.

3.4 Meta-Analysis of Drug-Induced PML Cases

Overall, there were 1017 PML events, reported in 42.71% of the included studies ($n = 44$). Among these, 70.45% included natalizumab in their treatment regimen ($n = 31$).

3.5 Natalizumab

A meta-analysis of 41 studies which reported at minimum the number of PML events, total number of patients and observation time showed an incidence of PML cases among patients diagnosed with multiple sclerosis who were undergoing natalizumab treatment according to standard interval dosing of 0.4 cases/100 persons (95% CI 0.36–0.44, $I^2 = 94\%$; $p < 0.001$), for a median observation period of 36 months (IQR 24–60 months) (mean 45.7, SD 28) (Fig. 2). The funnel plot assessing publication bias is presented in

Table 1 Distribution of pathologies described in included studies. Sum is above 103 as the same study may refer to more than one pathology

Pathology	Included studies (*n*)	% of overall included studies
Multiple sclerosis	71	68.93
Inflammatory bowel diseases	14	13.59
Kidney transplantation	6	5.82
Rheumatoid arthritis	5	4.85
Autoimmune thrombocytopenia	2	1.94
Systemic lupus erythematosus	2	1.94
Myasthenia gravis	1	0.97
Systemic sclerosis	1	0.97
Type I diabetes mellitus	1	0.97
NMDAR encephalitis	1	0.97
Opsoclonus-myoclonus-ataxia syndrome	1	0.97
Neuromyelitis optica	1	0.97
Granulomatosis with polyangiitis	1	0.97
Microscopic polyangiitis	1	0.97
Sjögren syndrome	1	0.97
Nephrotic syndrome	1	0.97
Dermatomyositis	1	0.97
Mixed connective tissue disorder	1	0.97

Fig. 3. Egger's test showed a significant small-study effect ($p < 0.001$).

3.5.1 Natalizumab—Mean/Median Time of Treatment and/or Number of Doses Only

When including in the meta-analysis only studies that reported the mean or median time of treatment ($n = 25$), and/or number of natalizumab doses, the incidence of PML cases was 0.33 cases/100 persons (95% CI 0.29–0.37, $I^2 = 50.04\%$; $p = 0.003$) (Fig. 4) for a median observation period of 44.1 months (IQR 28.4–60 months) (mean 50.3, SD 26.4) and a mean number of doses of 36.3 (SD 20.7). The funnel plot assessing publication bias is presented in Fig. 5. Egger's test showed a significant small-study effect ($p < 0.001$).

3.5.2 Natalizumab—Extended Interval Dosing and Standard Interval Dosing

Synthesizing studies that compared extended interval dosing with standard interval dosing, the incidence of PML cases was 0.08 cases/100 persons (95% CI 0.0–0.15, $I^2 = 0\%$; $p = 0.6$) (Fig. 6) for a mean observation period of 43.9 months (SD 21.2) and a mean number of doses of 31.7 (SD 15.8) for extended interval dosing, compared with 0.3 cases/100 persons (95% CI 0.25–0.34, $I^2 = 22.9\%$; $p = 0.26$) (Fig. 7) for a mean observation period of 31.4 months (SD 11.7) and a mean number of doses of 30.0 (9.8).

3.6 Fingolimod

A meta-analysis of eight studies showed an incidence of PML cases among patients diagnosed with MS who were undergoing fingolimod treatment of 0.01 cases/100 persons (95% CI 0.00–0.01, $I^2 = 91.9\%$; $p < 0.001$), for a median observation period of 47.6 months (IQR 31.62–53.85 months) (mean 44.5, SD 17.6) (Fig. 8).

When including in the meta-analysis only studies that reported the mean or median time of observation and treatment, the incidence of PML cases was 0.01 cases/100 persons (95% CI 0.00–0.01, $I^2 = 0.0\%$; $p = 0.820$) (Fig. 9) for a mean observation time of 40.9 months (SD 17.4) and a mean treatment duration of 39.2 months (SD 17.9).

3.7 Rituximab

The meta-analysis of 10 studies showed an incidence of PML cases among patients diagnosed with MS who were undergoing rituximab treatment of 0.01 cases/100 persons (95% CI −0.08 to 0.09, $I^2 = 20.4\%$; $p = 0.255$), for a median observation period of 23.5 months (IQR 22.1–42.1 months) (mean 28.1, SD 12.9) (Fig. 10).

3.8 Dimethyl Fumarate

A meta-analysis of three studies showed an incidence of PML cases among patients diagnosed with MS who were undergoing dimethyl fumarate treatment of 0.17 cases/100 persons (95% CI 0.12–0.22, $I^2 = 64.4\%$; $p = 0.06$), for a median observation period of 36.1 months (IQR 24–77.8 months) (mean 45.9, SD 28.2) (Fig. 11).

4 Discussion

In this study, we reviewed and meta-analyzed the risk of drug-induced PML in subjects affected by pathologies requiring immunosuppressive treatments, but not additionally immunocompromised by means of neoplasms, HIV or concomitant medications. This study intended to take into account globally drug-induced PML as reported by available literature, including a wide range of baseline pathologies and relative treatments, such as those affecting the gastrointestinal system, the central nervous system, rheumatologic disorders and in general diseases caused by dysregulation of the immune system.

Table 2 Overview of included observational studies with information about study design, baseline pathology, investigated drug(s), exposed population, PML cases and extract of Newcastle-Ottawa Scale total score

Study	Journal	Country	Study design	Baseline pathology	Investigated drug	Exposed population	PML cases	NOS
Afanasiev et al. (2017) [20]	*Neuromuscular Disorders*	France	Observational	Myasthenia gravis	Rituximab, prednisone	28	1	6
Alroughani et al. (2013) [21]	*Medical Principles and Practice*	Kuwait	Observational	Multiple sclerosis	IFN β-1a, IFN β-1b, natalizumab	38	0	5
Beldi-Ferchiou et al. (2020) [22]	*Multiple Sclerosis and Related Disorders*	France	Observational	Multiple sclerosis	Natalizumab	69	1	8
Bellizzi et al. (2011) [23]	*Journal of NeuroVirology*	Italy	Observational	Crohn's disease	Infliximab	18	0	8
Bellaguarda et al. (2015) [24]	*Clinical Gastroenterology and Hepatology*	USA	Observational	Crohn's disease	Natalizumab	38	0	5
Berger et al. (2018) [121]	*Neurology*	Multicenter	Pharmacovigilance	Multiple sclerosis	Fingolimod	1035	15	5
Bertrand et al. (2020) [25]	*Nephrology Dialysis Transplantation*	France	Observational	Kidney transplantation	Belatacept	280	2	4
Biernacki et al. (2022) [26]	*Plos One*	Hungary	Observational	Multiple sclerosis	Fingolimod	570	1	6
Butzkueven et al. (2014) [27]	*Journal of Neurology, Neurosurgery and Psychiatry*	Multicenter	Observational	Multiple sclerosis	Natalizumab	4821	18	5
Calabrese et al. (2017) [28]	*Journal of Neurology, Neurosurgery and Psychiatry*	Italy	Observational	Multiple sclerosis	Dimethyl fumarate (natalizumab)	39	0	6
Carotenuto A et al. (2017) [29]	*Journal of Neuroimmunology*	Italy	Observational	Multiple sclerosis	Natalizumab	52	1	4
Carruthers et al. (2014) [30]	*Multiple Sclerosis Journal*	USA	Observational	Multiple sclerosis	Natalizumab, glatiramer acetate, IFN β-1a, IFN β-1b, fingolimod	105	0	5
Chen et al. (2009) [31]	*The New England Journal of Medicine*	Israel	Observational	Multiple sclerosis	Natalizumab	19	0	7
Clerico et al. (2020) [32]	*Neurotherapeutics*	Italy	Observational	Multiple sclerosis	Natalizumab	360	0	7
Cobo-Calvo A et al. (2015) [33]	*European Neurology*	Spain	Observational	Multiple sclerosis	Natalizumab	70	0	5
Coerver et al. (2021) [34]	*Multiple Sclerosis and Related Disorders*	Netherlands	Observational	Multiple sclerosis	Natalizumab	253	5	5
Cohan et al. (2018) [35]	*Multiple Sclerosis and Related Disorders*	USA	Observational	Multiple sclerosis	Natalizumab, dimethyl fumarate	506	0	7
Correia et al. (2017) [36]	*International Immunopharmacology*	Portugal	Observational	Multiple sclerosis	Natalizumab	71	3	6
Dale et al. (2014) [37]	*Neurology*	Multicenter	Observational	NMDAR encephalitis, opsoclonus myoclonus ataxia syndrome, neuromyelitis optica spectrum disorders, neuropsychiatric systemic lupus erythematosus, other neuroinflammatory disorders	Rituximab	144	0	6

Table 2 (continued)

Study	Journal	Country	Study design	Baseline pathology	Investigated drug	Exposed population	PML cases	NOS
De Oliveira et al. (2015) [38]	*Arquivos de Neuro-psiquiatria*	Brazil	Observational	Multiple sclerosis	Natalizumab	75	1	6
Delbue et al. (2015) [39]	*Journal of Neurovirology*	Italy	Observational	Multiple sclerosis	Natalizumab	42	0	5
Dominguez-Mozo et al. (2017) [40]	*European Journal of Clinical Investigation*	Spain	Observational	Multiple sclerosis	Natalizumab	173	2	4
Dominguez-Mozo et al. (2016) [41]	*European Journal of Neurology*	Spain	Observational	Multiple sclerosis	Natalizumab	100	2	6
Foley et al. (2020) [42]	*Multiple Sclerosis and Related Disorders*	Multicenter	Observational	Multiple sclerosis	Natalizumab	6508	44	4
Gajofatto et al. (2014) [43]	*European Neurology*	Italy	Observational	Multiple sclerosis	Natalizumab, fingolimod	87	1	7
Giacoppo et al. (2017) [44]	*Medical Science Monitor*	Italy	Observational	Multiple sclerosis	Natalizumab	88	1	4
Giannecchini et al. (2012) [45]	*Journal of NeuroVirology*	Italy	Observational	Rheumatoid arthritis, systemic vasculitis, seronegative spondyloarthropathies	Infliximab	61	0	4
Ghezzi et al. (2015) [46]	*BMC Neurology*	Italy	Observational	Multiple sclerosis	Natalizumab	101	0	6
Gottenberg et al. (2010) [47]	*Arthritis and Rheumatism*	France	Observational	Rheumatoid arthritis	Rituximab	1272	0	5
Grinyó et al. (2010) [48]	*Transplantation*	Multicenter	Observational	Kidney transplant	Belatacept	1425	1	6
Guger et al. (2021) [49]	*Journal of Neurological Sciences*	Austria	Observational	Multiple sclerosis	Natalizumab	230	14	4
Holmén et al. (2011) [50]	*Multiple Sclerosis Journal*	Sweden	Observational	Multiple sclerosis	Natalizumab	1152	3	6
Huhn et al. (2018) [51]	*Journal of Neurology*	Germany	Observational	Multiple sclerosis	Alentuzumab (fingolimod)	50	0	3
Jaklin et al. (2021) [52]	*Frontiers in Neurology*	Norway	Observational	Multiple sclerosis	Natalizumab	66	1	6
Jilek et al. (2010) [53]	*The Lancet Neurology*	Switzerland	Observational	Multiple sclerosis	Natalizumab	24	0	6
Karanasios et al. (2021) [54]	*Multiple Sclerosis Journal-Experimental, Translational and Clinical*	Greece	Observational	Multiple sclerosis	Natalizumab	304	2	5
Leurs et al. (2018) [55]	*Multiple Sclerosis Journal*	Netherlands	Observational	Multiple sclerosis	Fingolimod (natalizumab)	52	0	6
Mancinelli et al. (2021) [56]	*Multiple Sclerosis Journal*	UK	Observational	Multiple sclerosis	Ocrelizumab (natalizumab)	42	0	7
Melin et al. (2012) [57]	*Journal of Neurological Sciences*	France	Observational	Multiple sclerosis	Natalizumab	180	0	6
Möhn et al. (2019) [58]	*Therapeutic Advances in Neurological Disorders*	Germany	Observational	Multiple sclerosis	Cladribine (natalizumab)	17	0	6
Moreira Ferreira et al. (2021) [59]	*Multiple Sclerosis Journal–Experimental, Translational and Clinical*	USA	Observational	Multiple sclerosis	Dimethyl fumarate, glatiramer acetate	88	0	7

Table 2 (continued)

Study	Journal	Country	Study design	Baseline pathology	Investigated drug	Exposed population	PML cases	NOS
Naegelin et al. (2018) [60]	*Multiple Sclerosis and Related Disorders*	Switzerland	Observational	Multiple sclerosis	Fingolimod (natalizumab)	25	0	6
Neff et al. (2008) [61]	*Transplantation*	USA	Observational	Kidney transplantation	Mycophenolate mofetil, steroids, tacrolimus, cyclosporine	25,511	9	5
Oshima et al. (2019) [9]	*Multiple Sclerosis Journal*	Multicenter	Observational	Multiple sclerosis	Natalizumab, fingolimod, dimethyl fumarate, dalfampridine, rituximab, glatiramer acetate, IFN	100,921	786	2
Outteryck et al. (2014) [62]	*European Journal of Neurology*	France	Observational	Multiple sclerosis	Natalizumab	1204	6	6
Parikh et al. (2013) [63]	*Inflammatory Bowel Diseases*	Multicenter	Observational	IBD	Vedolizumab	72	0	7
Parikh et al. (2018) [64]	*Drug Safety*	Multicenter	Observational	IBD	Vedolizumab	2884	0	7
Patel et al. 2012 [65]	*Blood*	Multicenter	Observational	Immune thrombocytopenia	Rituximab	138	0	5
Pato Pato et al. (2020) [66]	*Neurologia*	Spain	Observational	Multiple sclerosis	Natalizumab	89	1	4
Prezioso et al. (2021) [67]	*Viruses*	Italy	Observational	Multiple sclerosis	Ocrelizumab	42	0	6
Prockl et al. (2020) [68]	*Journal of the Neurological Sciences*	Germany	Observational	Multiple sclerosis	Ocrelizumab	128	0	6
Prosperini et al. (2016) [69]	*Journal of Neurological Sciences*	Italy	Observational	Multiple sclerosis	Natalizumab	152	1	4
Rauer et al. (2020) [70]	*Clinical Neurology and Neurosurgery*	Germany	Observational	Multiple sclerosis	Ocrelizumab	489	1	6
Reboursiere et al. (2016) [71]	*International Journal of Hematology*	France	Observational	Immune thrombocytopenia	Rituximab	35	0	5
Rempe et al. (2020) [72]	*Multiple Sclerosis Journal–Experimental, Translational and Clinical*	USA	Observational	Multiple sclerosis	Ocrelizumab, dimethyl fumarate, IFN, glatiramer acetate, natalizumab, teriflunomide, fingolimod, daclizumab	45	0	4
Raffel et al. (2015) [73]	*Multiple Sclerosis Journal*	UK	Observational	Multiple sclerosis	Natalizumab	485	2	6
Riancho et al. (2021) [74]	*Frontiers in Immunology*	Spain	Observational	Multiple sclerosis	Natalizumab	39	0	5
Rinaldi et al. (2010) [75]	*Journal of Neurology, Neurosurgery and Psychiatry*	Italy	Observational	Multiple sclerosis	Natalizumab	42	0	7
Rodríguez de Castro et al. (2021) [76]	*European Journal of Hospital Pharmacy*	Spain	Observational	Multiple sclerosis	Natalizumab, fingolimod, glatiramer acetate, IFN	19	0	7
Ryerson et al. (2016) [77]	*Journal of Neurology, Neurosurgery and Psychiatry*	USA	Observational	Multiple sclerosis	Natalizumab	1974	4	5
Ryerson et al. (2019) [78]	*Neurology*	Multicenter	Observational	Multiple sclerosis	Natalizumab	35,521	13	5
Saida et al. (2017) [79]	*Neurology and Therapy*	Japan	Observational	Multiple sclerosis	Natalizumab	106	0	4

Table 2 (continued)

Study	Journal	Country	Study design	Baseline pathology	Investigated drug	Exposed population	PML cases	NOS
Salzer et al. (2016) [80]	*Neurology*	Sweden	Observational	Multiple sclerosis	Rituximab	822	0	7
Sarsour et al. (2020) [81]	*Pharmacology Research & Perspectives*	Multicenter	Observational	Rheumatoid arthritis, granulomatosis with polyangiitis, microscopic polyangiitis, systemic lupus erythematosus, Sjögren's syndrome, systemic vasculitis, eosinophilic granulomatosis with polyangiitis, polydermatomyositis, mixed connective tissue disease, nephrotic syndrome	Rituximab	998	0	9
Singh et al. (2016) [82]	*Journal of Pediatric Gastroenterology and Nutrition*	USA	Observational	Crohn's disease	Natalizumab	9	0	5
Sousa et al. (2014) [83]	*Revista de neurologia*	Portugal	Observational	Multiple sclerosis	Natalizumab	383	2	6
Tanaka et al. (2020) [84]	*Clinical and Experimental Neuroimmunology*	Japan	Observational	Multiple sclerosis	Fingolimod	24	0	4
Trampe et al. (2012) [85]	*Neurology*	Germany	Observational	Multiple sclerosis	Natalizumab	2180	10	5
Uleri et al. (2016) [86]	*Journal of Neurovirology*	Italy	Observational	Multiple sclerosis	Natalizumab, fingolimod	39	0	8
Van Lierop et al. (2021) [87]	*Multiple Sclerosis Journal-Experimental, Translational and Clinical*	Netherlands	Observational	Multiple sclerosis	Ocrelizumab (natalizumab)	42	2	5
Van Pesch et al. (2014) [88]	*Acta Neurological Belgica*	Multicenter	Observational	Multiple sclerosis	Natalizumab	563	2	6
Vennegoor et al. (2015) [89]	*Multiple Sclerosis Journal*	Netherlands	Observational	Multiple sclerosis	Natalizumab	193	4	6
Vukusic et al. (2020) [90]	*JAMA Neurology*	France	Observational	Multiple sclerosis	Natalizumab	6318	45	6
Yamout et al. (2018) [91]	*Journal of Immunology Research*	Lebanon	Observational	Multiple sclerosis	Rituximab	89	0	5
Zanghì et al. (2021) [92]	*Neurotherapeutics*	Italy	Observational	Multiple sclerosis	Ocrelizumab, rituximab, cladribrine (natalizumab)	120	0	7
Ziemssen et al. (2020) [93]	*Multiple Sclerosis and Related Disorders*	Germany	Observational	Multiple sclerosis	Natalizumab, fingolimod	3912	1	6
Zivadinov et al. (2012) [94]	*Multiple Sclerosis Journal*	USA	Observational	Multiple sclerosis	Natalizumab, IFN	68	1	6

Drugs between parentheses indicate previous treatment exposure of the described population

IBD inflammatory bowel disease, *IFN* interferon, *NOS* Newcastle-Ottawa Scale, *PML* progressive multifocal leukoencephalopathy

Table 3 Overview of included RCT studies, with information about study design, baseline pathology, investigated drug(s), exposed population, PML cases, extract of RoB2 score

Author (year) [ref]	Journal	Country	Study design	Baseline pathology	Investigated drug	Exposed population	PML cases	RoB2
Albano et al. (2013) [96]	*Transplantation*	Multicenter	RCT	Kidney transplantation	Tacrolimus, basiliximab	1153	0	SC
Clerico et al. (2014) [95]	*JAMA Neurology*	Italy	RCT	Multiple sclerosis	Natalizumab	124	1	H
Confavreux et al. (2012) [97]	*Multiple Sclerosis Journal*	Multicenter	RCT	Multiple sclerosis	Teriflunomide	147	0	SC
Feagan et al. (2008) [98]	*Clinical Gastroenterology and Hepatology*	USA	RCT	Crohn's disease	Vedolizumab	127	0	H
Foley et al. (2022) [120]	*The Lancet Neurology*	Multicenter	RCT	Multiple sclerosis	Natalizumab	499	1	L
Giovannoni et al. (2018) [99]	*Multiple Sclerosis Journal*	Multicenter	RCT	Multiple sclerosis	Daclizumab beta, IFN β-1a	1841	0	SC
Hibi et al. (2019) [100]	*Intestinal Research*	Japan	RCT	Ulcerative colitis	Abrilumab	45	0	SC
Klintmalm et al. (2014) [101]	*American Journal of Transplantation*	Multicenter	RCT	Kidney transplantation	Tacrolimus, mycophenolate mofetil, belatacept, basiliximab	250	1	SC
Mehta et al. (2019) [102]	*Neurology*	Multicenter	RCT	Multiple sclerosis	Dimethyl fumarate	1736	1	H
Miller et al. (2012) [103]	*The Lancet Neurology*	Multicenter	RCT	Multiple sclerosis	Firategrast	343	0	SC
Ng et al. (2018) [104]	*Inflammatory Bowel Diseases*	Multicenter	RCT	IBD	Vedolizumab	2243	0	H
Pescovitz et al. (2009) [105]	*The New England Journal of Medicine*	Multicenter	RCT	Diabetes type 1	Rituximab	52	0	H
Reinisch et al. (2021) [106]	*Journal of Crohn's & Colitis*	Multicenter	RCT	Ulcerative colitis	Ontamalimab	330	0	H
Rigby et al. (2012) [107]	*Arthritis and Rheumatism*	Multicenter	RCT	Rheumatoid arthritis	Ocrelizumab	686	0	SC
Rudick et al. (2006) [108]	*New England Journal of Medicine*	Multicenter	RCT	Multiple sclerosis	IFN β-1a, natalizumab	589	2	SC
Saida et al. (2017) [109]	*Neurology and Therapy*	Japan	RCT	Multiple sclerosis	Natalizumab	39	0	H
Sandborn et al. (2005) [110]	*The New England Journal of Medicine*	Multicenter	RCT	Crohn's disease	Natalizumab	762	1	SC
Sandborn et al. (2019) [111]	*Gastroenterology*	Multicenter	RCT	Ulcerative colitis	Abrilumab	238	0	L
Sands et al. (2014) [112]	*Gastroenterology*	Multicenter	RCT	Crohn's disease	Vedolizumab	209	0	SC
Schiopu et al. (2016) [113]	*Arthritis Research & Therapy*	Multicenter	RCT	Systemic sclerosis	Inebilizumab	24	0	L
Tak et al. (2011) [114]	*Annals of the Rheumatic Diseases*	Multicenter	RCT	Rheumatoid arthritis	Rituximab	499	0	L
Targan et al. (2007) [115]	*Gastroenterology*	Multicenter	RCT	Crohn's disease	Natalizumab	259	0	SC
Van Kempen et al. (2020) [116]	*Neurology*	Netherlands	RCT	Multiple sclerosis	Natalizumab	61	0	H

Table 3 (continued)

Author (year) [ref]	Journal	Country	Study design	Baseline pathology	Investigated drug	Exposed population	PML cases	RoB2
Vo et al. (2008) [117]	*The New England Journal of Medicine*	USA	RCT	Kidney transplantation	Rituximab, IVIG	20	0	H
Wallace et al. (2019) [118]	*Arthritis & Rheumatology*	Multicenter	RCT	Systemic lupus erythematosus	Belimumab	96	0	H
Wang et al. (2020) [119]	*Journal of Clinical Pharmacology*	Multicenter	RCT	IBD	Ontamalimab	304	0	L

H high risk of bias, *IBD* inflammatory bowel disease, *IFN* interferon, *IVIG* intravenous immunoglobulins, *L* low risk of bias, *PML* progressive multifocal leukoencephalopathy, *RCT* randomized controlled trial, *RoB2* Risk of Bias tool 2 total score, *SC* some concern of bias

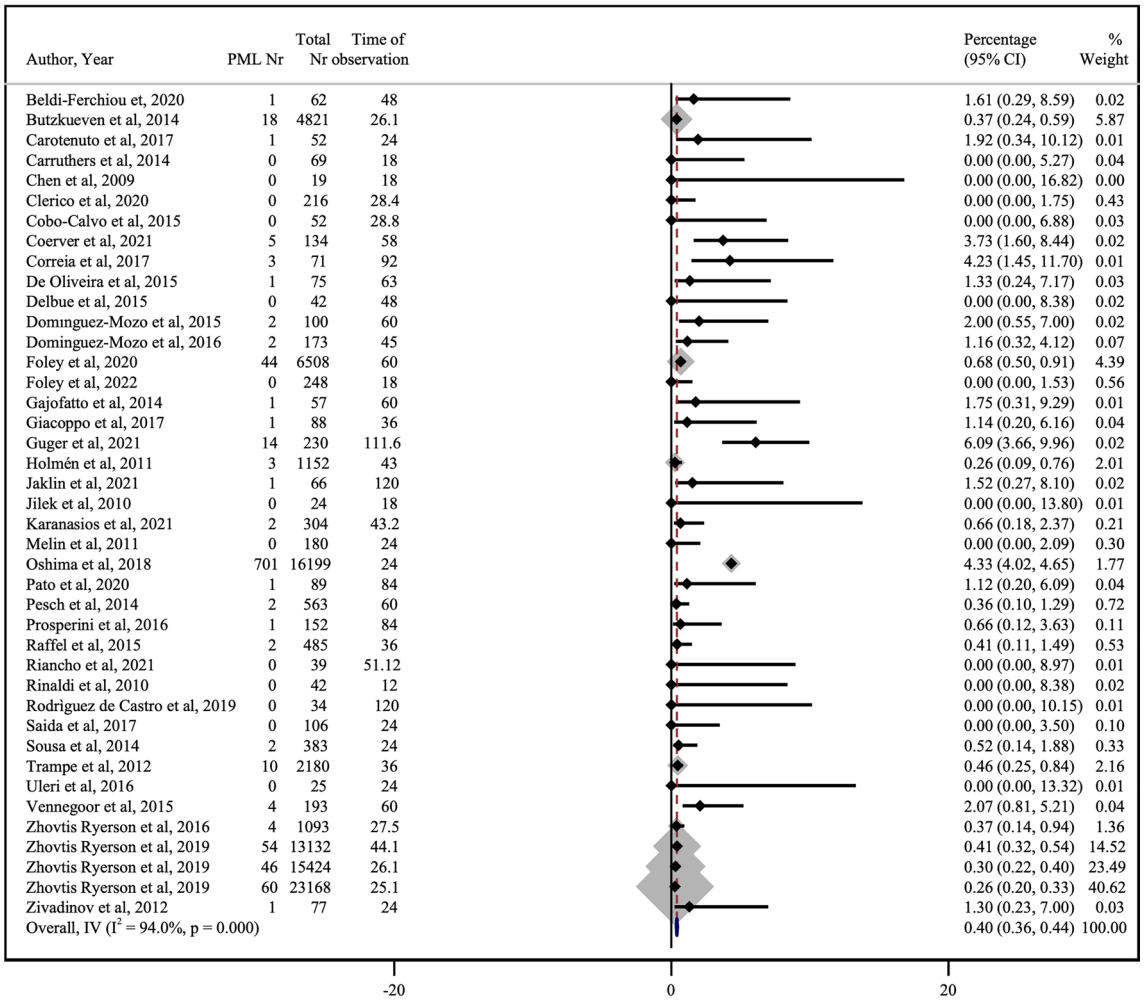

Fig. 2 Meta-analysis for all included studies concerning natalizumab-induced risk of progressive multifocal leukoencephalopathy (PML). The horizontal *x*-axis is the incidence of PML among referenced studies. Horizontal lines represent confidence interval (CI), black points represent the risk of PML development as calculated for each record. The grey diamond represents the weight of the included study in terms of population. The blue diamond represents the meta-analysis for overall risk of PML development after drug exposure

Studies reporting the use of unclear or combined therapy were excluded from the meta-analysis such as in the case of interferon, for which we found no eligible case of PML reported, unless co-administered or administered shortly after a natalizumab-based regimen. Furthermore, no included study reported any case of PML during follow-up

or treatment with ocrelizumab, vedolizumab, abrilumab, ontamalimab, teriflunomide, daclizumab, inebilizumab, basiliximab, tacrolimus, belimumab, infliximab, firategrast, disulone, azathioprine or danazole. However, literature reports cases of PML during treatment with one or more of the above-mentioned drugs, such as in the case of ocrelizumab, tacrolimus or inebilizumab [122, 123], the latter being listed as cause of a possible PML case in a deceased patient during an inebilizumab clinical trial [124]. However, these and similar reports were not included in the present study as they did not meet our inclusion criteria.

As for dalfampridine, all 50 cases of PML found were described by a single study [9]. Nevertheless, as the authors clarify in their study, 46 of 50 PML patients were previously treated with natalizumab, making it possible, if not likely, that there was a carryover effect after natalizumab administration. On a similar note, the same study also reports 24 cases of PML during or after glatiramer acetate treatment. We decided to exclude data about these two drugs from our meta-analysis, considering also their mechanism of action [125, 126]. Nevertheless, we included all data from the mentioned study in the systematic review (Tables 2, 3).

When considering the risk of PML in the drug-exposed population, dalfampridine, glatiramer acetate, dimethyl fumarate and fingolimod show a relatively safe profile, with only a few studies reporting events of PML in the treated population, mostly due to carry-over risk from previous treatment. Regardless of the specifics of each single included report, the meta-analysis reduces the risk of drawing misguided conclusions, even when data were lacking, such as in the case of records not reporting the entire treatment history for all included patients.

Besides that already stated for dimethyl fumarate, it is worth mentioning that the reported results may be largely influenced by the effect of single studies, and even though this drug appears relatively safe in terms of PML events, we could not obtain the necessary information about the specific known risk factors for the development of PML during dimethyl fumarate treatment, such as absolute lymphocyte count for all cases [127]. The sub-analysis for this kind of data, although fundamental, could be applicable *mutatis mutandis* to all discussed drugs. Nevertheless, this appeared beyond the purpose and design of our study.

As for rituximab, our results apply in the limited setting of our included population. This may be a limitation, since our results may not be generalizable to the whole population undergoing treatment with rituximab, but it could also provide an interesting point of view about this drug, as our data focus solely on the drug influence on PML risk. This may be useful in a comparison of this risk with that of the hematological population undergoing rituximab treatment, where both the drug and the pathology itself may act as a strong immunosuppressive stimulus, possibly in a synergistic manner. Once more, this aspect was beyond the purpose of our study.

As previously mentioned, we could not include single studies in the meta-analysis. This is the case for the nine and four cases of PML described after treatment with mycophenolate mofetil and belatacept, respectively. Nevertheless, data about these cases is available as part of our systematic review (Tables 2, 3).

Our meta-analysis showed treatment with natalizumab carries a risk for the development of PML of 0.33 cases/100 persons (95% CI 0.29–0.37), for a median observation period of 36 months (IQR 26.1–60 months) (mean 47.7, SD 25.7) and a mean number of doses of 33.5 (SD 14). Nevertheless, the FDA Adverse Event Reporting System (FAERS) counts a total of 1914, which is

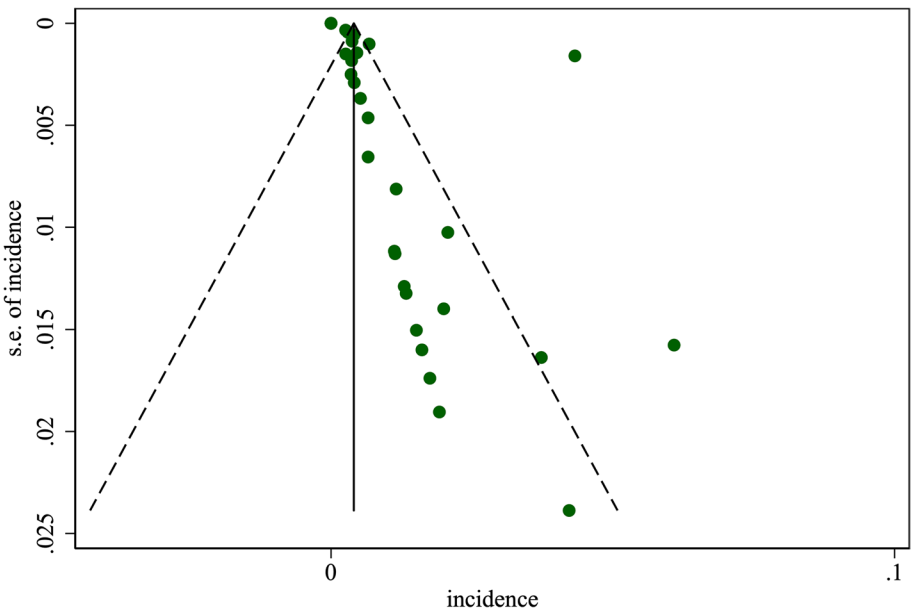

Fig. 3 Funnel plot with pseudo 95% confidence limits, assessing publication bias for studies depicted in Fig. 2. The horizontal *x*-axis is the incidence of progressive multifocal leukoencephalopathy (PML) among referenced studies. *s.e.* standard error

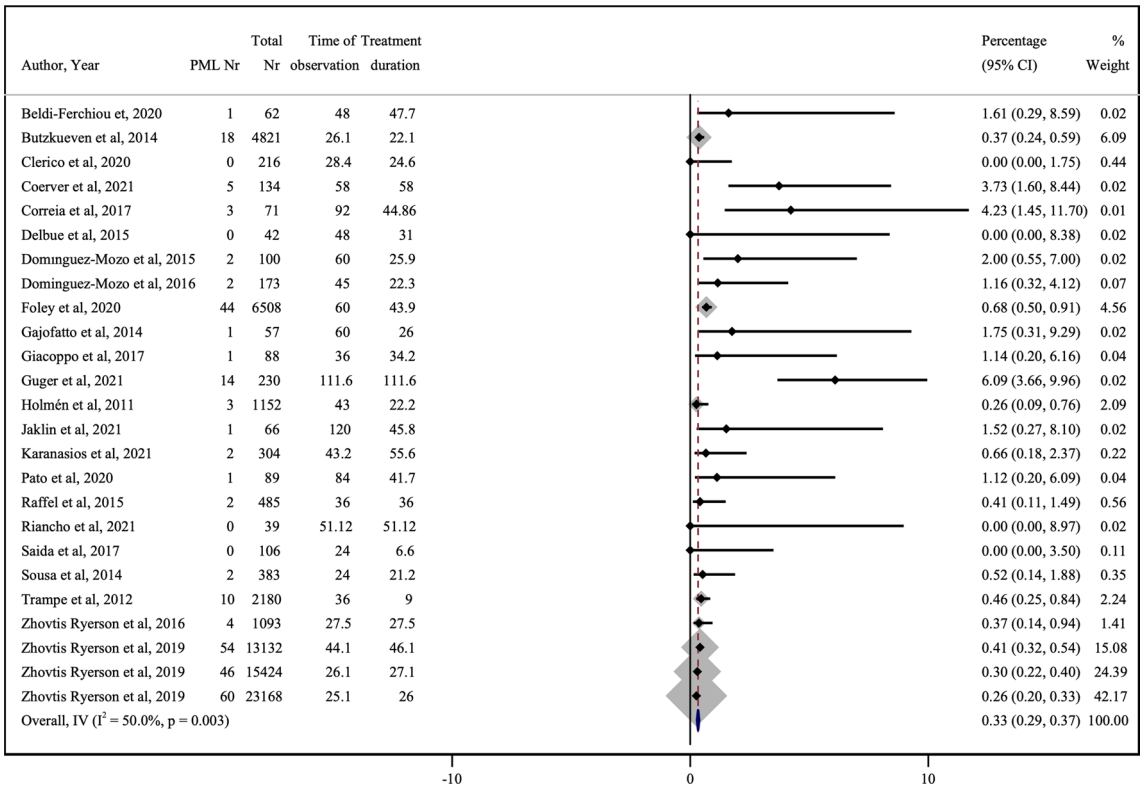

Fig. 4 Meta-analysis for studies concerning natalizumab-induced risk of progressive multifocal leukoencephalopathy (PML), limiting results to those studies reporting treatment duration and/or number of administered doses for the included population. The horizontal *x*-axis is the incidence of PML among referenced studies. Horizontal lines represent confidence interval (CI), black points represent the risk of PML development as calculated for each record. The grey diamond represents the weight of the included study in terms of population. The blue diamond represents the meta-analysis for overall risk of PML development after drug exposure

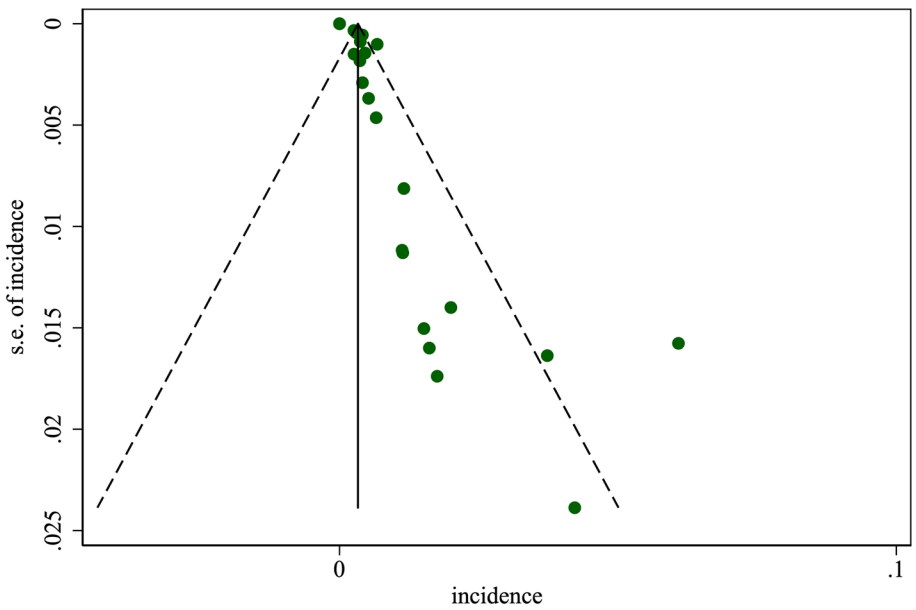

Fig. 5 Funnel plot with pseudo 95% confidence limits assessing publication bias for studies depicted in Fig. 4. The horizontal *x*-axis is the incidence of progressive multifocal leukoencephalopathy (PML) among referenced studies

more than the cases reported in our systematic review and meta-analysis [128]. Reasons for this discrepancy include ineligible study design, lack of clinical data (e.g. treatment duration, mean number of doses administered), lack of published reports, ineligible population, presence of confounders such as carry-over therapy, advanced age

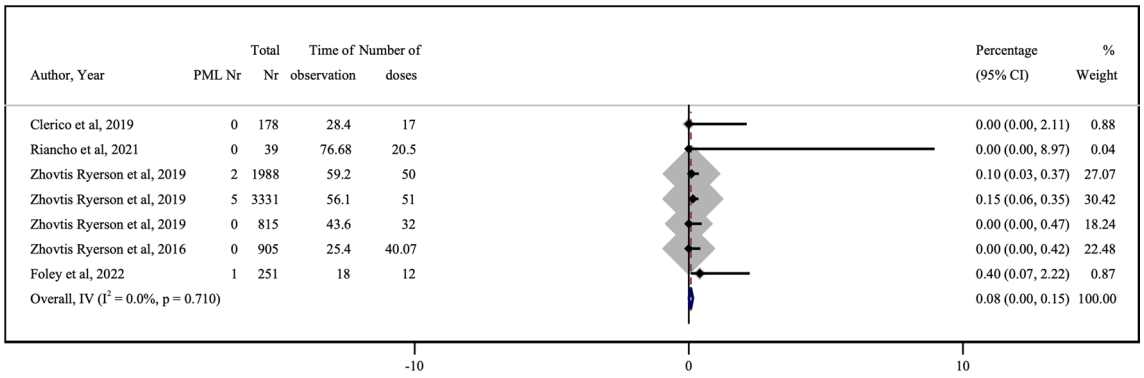

Fig. 6 Meta-analysis for studies concerning natalizumab-induced risk of progressive multifocal leukoencephalopathy (PML) when infused as extended interval dosing. The horizontal *x*-axis is the incidence of PML among referenced studies. Horizontal lines represent confidence intervals (CI), black points represent the risk of PML development as calculated for each record. The grey diamond represents the weight of the included study in terms of population. The blue diamond represents the meta-analysis for overall risk of PML development after drug exposure

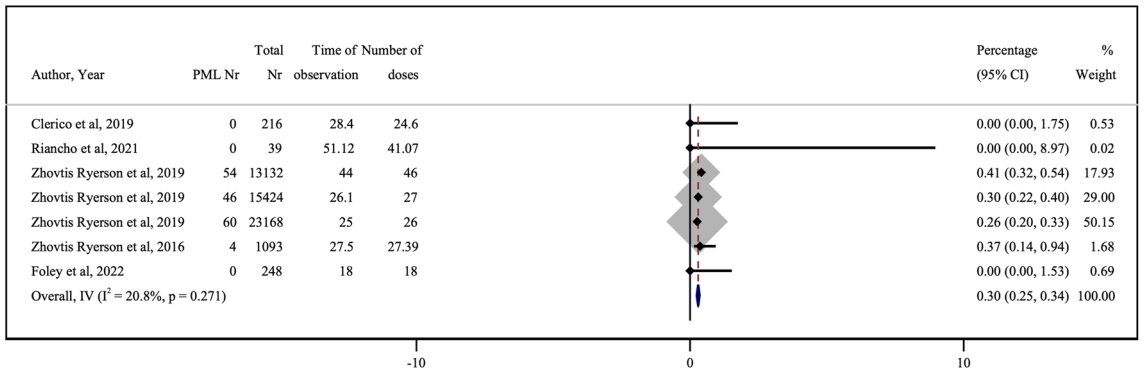

Fig. 7 Meta-analysis for studies concerning natalizumab-induced risk of progressive multifocal leukoencephalopathy (PML) when infused as standard interval dosing. The horizontal *x*-axis is the incidence of PML among referenced studies. Horizontal lines represent confidence intervals (CI), black points represent the risk of PML development as calculated for each record. The grey diamond represents the weight of the included study in terms of population. The blue diamond represents the meta-analysis for overall risk of PML development after drug exposure

and other immunosuppressive treatment. According to the extremely limited data available, it could be safe to assume there is a difference in risk according to the infusion protocol used, as depicted by our meta-analysis comparing data about patients treated with standard interval dosing and extended interval dosing. When risk of PML is calculated among extended or standard infusion dosing patients only, extended interval dosing-related risk appears to be smaller, that is, 0.07 cases/100 persons (95% CI 0.0–0.15) for a mean observation period of 48.2 months (SD 19.6) and a mean number of doses of 35.1 (SD 14.5) compared with 0.3 cases/100 persons (95% CI 0.25–0.34), for a mean observation period of 33.7 months (SD 11.1) and a mean number of doses of 32.0 (SD 9.1). The compared efficacy of these two regimens and clinical response evaluation was beyond the purpose of the present study. Our search strategy was designed to include all solid organ transplant patients. Nevertheless, few records, all concerning kidney transplant patients, fulfilled our inclusion criteria and reported useful data for our analysis. We decided to proceed with our analysis of the eligible records in accordance with our initial inclusion criteria even though we acknowledge the population of solid organ transplant patients might be underrepresented.

4.1 Strengths and Limitations of the Present Study

To our knowledge, this is the first systematic review and meta-analysis aimed at collectively describing all drug-induced PML in individuals exposed to immunosuppressants, but whose immune system is not additionally suppressed by means of neoplasms, concomitant medications

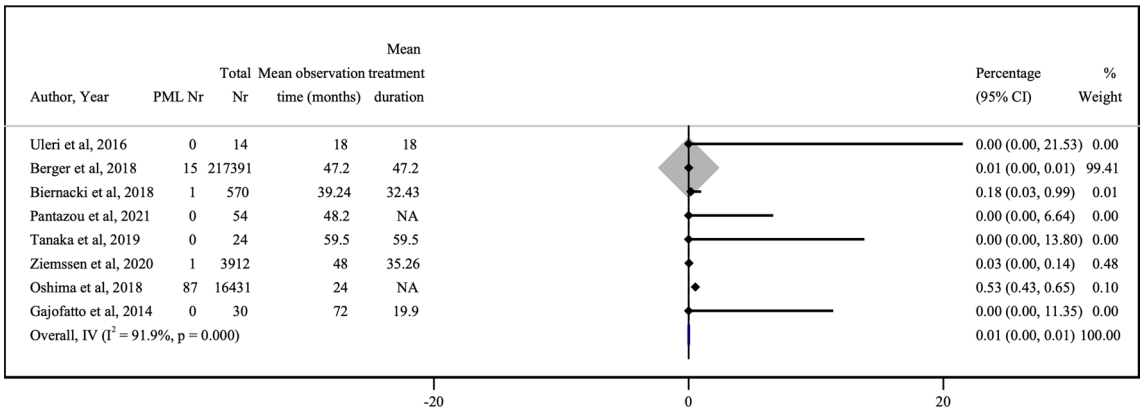

Fig. 8 Meta-analysis for all included studies concerning fingolimod-induced risk of progressive multifocal leukoencephalopathy (PML). The horizontal *x*-axis is the incidence of PML among referenced studies. Horizontal lines represent confidence intervals (CI), black points represent the risk of PML development as calculated for each record. The grey diamond represents the weight of the included study in terms of population. The blue diamond represents the meta-analysis for overall risk of PML development after drug exposure

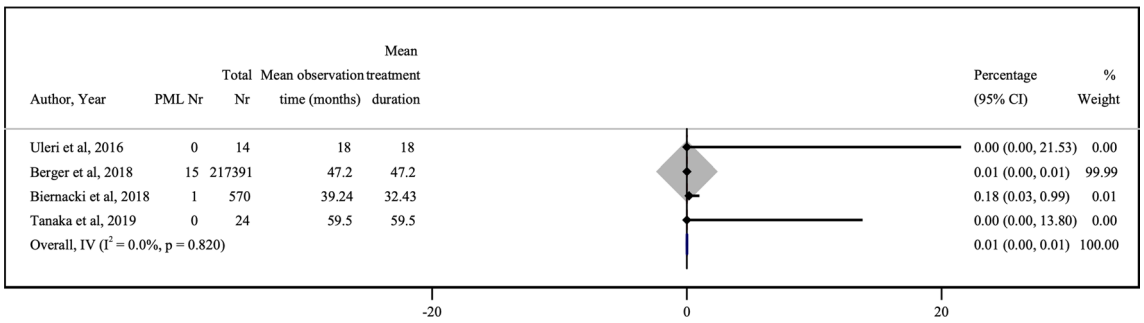

Fig. 9 Meta-analysis for all included studies concerning fingolimod-induced risk of progressive multifocal leukoencephalopathy (PML), limiting results to those reporting observation time and treatment duration. The horizontal *x*-axis is the incidence of PML among referenced studies. Horizontal lines represent confidence intervals (CI), black points represent the risk of PML development as calculated for each record. The grey diamond represents the weight of the included study in terms of population. The blue diamond represents the meta-analysis for overall risk of PML development after drug exposure

or HIV, without restricting the search to specific drugs or to specific pathologies. In order to do so, great effort was made to retrieve all relevant literature from inception, in all languages. In order to include high quality research, we excluded case reports and case series from our analysis. However, as a result, the occurrence of PML during treatment with some of the above-mentioned drugs was not included. At the same time, this could represent both a strength and a limitation of the present study. In this work we considered as immunocompetent any patient without solid organ tumor, hematologic malignancies, HIV, or primary immunodeficiency. Nevertheless, we acknowledge some autoimmune disease, such as sarcoidosis, could itself be associated with a certain degree of autoimmune dysregulation [129].

The present study also presents several limitations that are important to discuss to ensure a better understanding of the results. Firstly, data from included studies were frequently insufficient or unclear. This was particularly limiting in the case of observation time. While some studies reported observation time after drug administration as follow-up time, others ambiguously reported follow-up data as 'treatment duration', 'study period' or other unprecise indications. Another example of this issue was represented by the lack of information about JCV serostatus/JCV index in included literature. When extracting such data, we found it to be sparse and most often lacking, making it impossible to include and to meta-analyze. Even if the present record mentions no information about this issue, we acknowledge its clinical relevance in PML risk calculation and invite the reader to consider it as a limitation of the review [12, 130]. When data were unclear, we used the safest assumption available. Nevertheless, this may have altered the results to an unpredictable extent. Concerning reported cases of drug-associated PML, discrepancies in numbers between our results and those reported elsewhere could be due to multiple

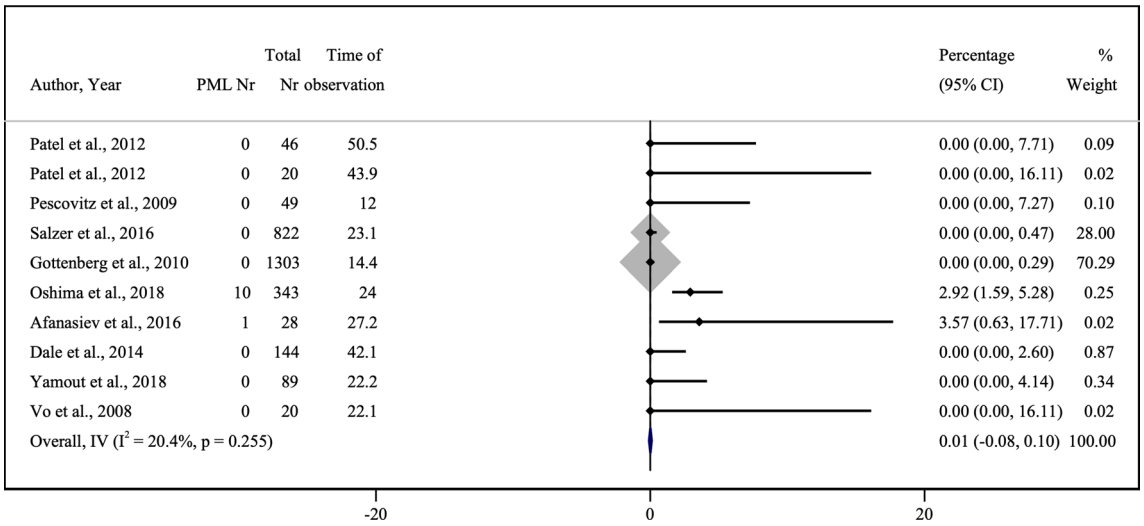

Fig. 10 Meta-analysis for all included studies concerning rituximab-induced risk of progressive multifocal leukoencephalopathy (PML). The horizontal *x*-axis is the incidence of PML among referenced studies. Horizontal lines represent confidence intervals (CI), black points represent the risk of PML development as calculated for each record. The grey diamond represents the weight of the included study in terms of population. The blue diamond represents the meta-analysis for overall risk of PML development after drug exposure.

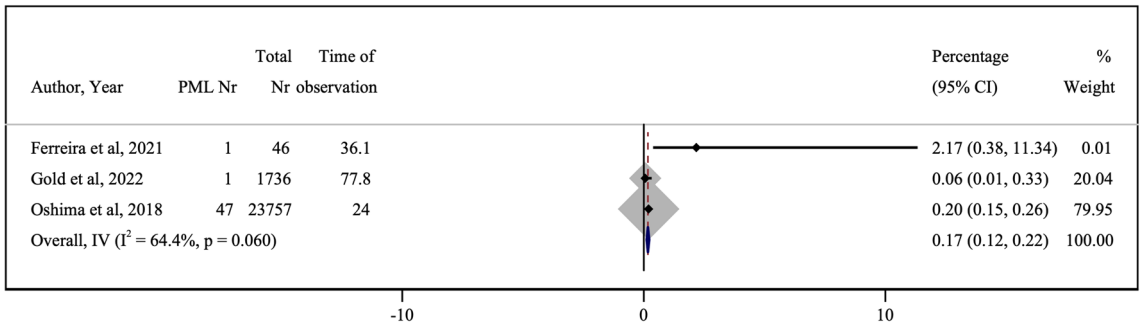

Fig. 11 Meta-analysis for all included studies concerning dimethyl fumarate-induced risk of progressive multifocal leukoencephalopathy (PML). The horizontal *x*-axis is the incidence of PML among referenced studies. Horizontal lines represent confidence intervals (CI), black points represent the risk of PML development as calculated for each record. The grey diamond represents the weight of the included study in terms of population. The blue diamond represents the meta-analysis for overall risk of PML development after drug exposure.

reasons, such as ineligibility of study design, lack of clinical pharmacological data, unavailability of published reports, ineligibility of population due to confounding factors such as age and previous or multiple immunosuppressive treatment. Furthermore, many records had to be excluded due to the lack of an overall drug-exposed population, making an assessment of the risk impossible. These records were therefore excluded from our analysis.

Another element to consider is that malignancies were excluded from the present review and meta-analysis. While this was intended to focus the attention solely on the contribution of immunosuppressants in the development of PML, it is worth considering that results found in the present record may not reflect either the totality, nor the majority of the patients undergoing treatment with drugs such as rituximab, most often used in a very diverse subset of patients from the one included here.

Funnel plot analysis found publication bias, which could be a result of having found, and therefore included, only peer-reviewed studies. Otherwise, this could result from the heterogeneity of included studies. It could be useful to report, though, that a great proportion of data was obtained by registrative studies run by pharmaceutical companies. However, as previously discussed by Page et al., funnel plots should be seen as a generic means of examining *small study effect*, hence the tendency for the smaller studies in a meta-analysis to show larger treatment effects, and not as a tool to diagnose bias, since several factors may lead to asymmetry in a funnel plot [131].

5 Conclusions

A high risk of drug-related PML in the not otherwise immunosuppressed population is found in the neurological field. This risk is higher during multiple sclerosis treatment, and highest during long-term natalizumab therapy. Although this drug is still routinely prescribed in this field, in other areas, such as inflammatory bowel diseases, it could play a progressively smaller role, and be gradually replaced by other more recently approved agents, such as vedolizumab, for which we found no reported case of PML. In other areas of medicine, where the use of modern targeted therapy already plays an important role, the risk of drug-induced PML is much less permeating.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40264-023-01383-4.

Declarations

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Author contributions MI and LVR designed the study. LVR, NB, IF, RI, BM, FDM, DK and VB performed the literature search and extracted data from the identified articles. MI, VM and LS validated record selection, risk of bias evaluation and extracted data. DZ conducted the meta-analyses and, together with LVR, NB, RI and MI, drafted the manuscript. All authors reviewed the manuscript, contributed to its revision, and approved the final version submitted.

References

1. Maginnis MS, Atwood WJ. JC Virus: an oncogenic virus in animals and humans? Semin Cancer Biol. 2009;19:261–9.
2. Cortese I, Reich DS, Nath A. Progressive multifocal leukoencephalopathy and the spectrum of JC virus-related disease. Nat Rev Neurol. 2021;17:37–51.
3. Khalili A, Craigie M, Donadoni M, Sariyer IK. Host-immune interactions in JC virus reactivation and development of progressive multifocal leukoencephalopathy (PML). J Neuroimmune Pharmacol. 2019;14:649–60.
4. Miyamura T, Jikuya H, Soeda E, Yoshiike K. Genomic structure of human polyoma virus JC: nucleotide sequence of the region containing replication origin and small-T-antigen gene. J Virol. 1983;45:73.
5. Gosert R, Kardas P, Major EO, Hirsch HH. Rearranged JC virus noncoding control regions found in progressive multifocal leukoencephalopathy patient samples increase virus early gene expression and replication rate. J Virol. 2010;84:10448–56.
6. Ciardi MR, Zingaropoli MA, Iannetta M, Prezioso C, Perri V, Pasculli P, et al. JCPyV NCCR analysis in PML patients with different risk factors: exploring common rearrangements as essential changes for neuropathogenesis. Virol J. 2020;17:23.
7. Tan CS, Koralnik IJ. Progressive multifocal leukoencephalopathy and other disorders caused by JC virus: clinical features and pathogenesis. Lancet Neurol. 2010;9:425–37.
8. Hatchwell E, Smith EB, Jalilzadeh S, Bruno CD, Taoufik Y, Hendel-Chavez H, et al. Progressive multifocal leukoencephalopathy genetic risk variants for pharmacovigilance of immunosuppressant therapies. Front Neurol. 2022;13:1016377.
9. Oshima Y, Tanimoto T, Yuji K, Tojo A. Drug-associated progressive multifocal leukoencephalopathy in multiple sclerosis patients. Mult Scler J. 2019;25:1141–9.
10. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;2021:n71.
11. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. Syst Rev. 2016;5:210.
12. Ferenczy MW, Marshall LJ, Nelson CDS, Atwood WJ, Nath A, Khalili K, et al. Molecular biology, epidemiology, and pathogenesis of progressive multifocal leukoencephalopathy, the JC virus-induced demyelinating disease of the human brain. Clin Microbiol Rev. 2012;25:471–506.
13. Gheuens S, Pierone G, Peeters P, Koralnik IJ. Progressive multifocal leukoencephalopathy in individuals with minimal or occult immunosuppression. J Neurol Neurosurg Psychiatry. 2010;81:247–54.
14. Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. Stat Methods Med Res. 2018;27:1785–805.
15. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014;14:135.
16. Higgins JPT. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557–60.
17. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629–34.
18. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;l4898.
19. Lo CK-L, Mertz D, Loeb M. Newcastle-Ottawa Scale: comparing reviewers' to authors' assessments. BMC Med Res Methodol. 2014;14:45.
20. Afanasiev V, Demeret S, Bolgert F, Eymard B, Laforêt P, Benveniste O. Resistant myasthenia gravis and rituximab: a monocentric retrospective study of 28 patients. Neuromuscul Disord. 2017;27:251–8.
21. Alroughani R, Al Hashel J, Thussu A, Ahmed SF. Use of natalizumab in patients with active relapsing-remitting multiple sclerosis in Kuwait. Med Princ Pract. 2013;22:495–9.
22. Beldi-Ferchiou A, Wahab A, Duchmann M, Hodel J, Patry I, Delfau-Larue M-H, et al. High effector-memory CD8+ T-cell

levels correlate with high PML risk in natalizumab-treated patients. Mult Scler Relat Disord [Internet]. 2020;46. https://www.embase.com/search/results?subaction=viewrecord&id=L2007651415&from=export
23. Bellizzi A, Anzivino E, Ferrari F, Di Nardo G, Colosimo MT, Fioriti D, et al. Polyomavirus JC reactivation and noncoding control region sequence analysis in pediatric Crohn's disease patients treated with infliximab. J Neurovirol. 2011;17:303–13.
24. Bellaguarda E, Keyashian K, Pekow J, Rubin DT, Cohen RD, Sakuraba A. Prevalence of antibodies against JC virus in patients with refractory Crohn's disease and effects of natalizumab therapy. Clin Gastroenterol Hepatol. 2015;13:1919–25.
25. Bertrand D, Chavarot N, Gatault P, Garrouste C, Bouvier N, Grall-Jezequel A, et al. Opportunistic infections after conversion to belatacept in kidney transplantation. Nephrol Dial Transpl. 2020;35:336–45.
26. Biernacki T, Sandi D, Füvesi J, Fricska-Nagy Z, Kincses TZ, Ács P, et al. The safety and efficacy of fingolimod: Real-world data from a long-term, non-interventional study on the treatment of RRMS patients spanning up to 5 years from Hungary. PLoS ONE [Internet]. 2022;17. https://www.embase.com/search/results?subaction=viewrecord&id=L2017817195&from=export.
27. Butzkueven H, Kappos L, Pellegrini F, Trojano M, Wiendl H, Patel RN, et al. Efficacy and safety of natalizumab in multiple sclerosis: Interim observational programme results. J Neurol Neurosurg Psychiatry. 2014;85:1190–7.
28. Calabrese M, Pitteri M, Farina G, Bajrami A, Castellaro M, Magliozzi R, et al. Dimethyl fumarate: a possible exit strategy from natalizumab treatment in patients with multiple sclerosis at risk for severe adverse events. J Neurol Neurosurg Psychiatry. 2017;88:1073–8.
29. Carotenuto A, Scalia G, Ausiello F, Moccia M, Russo CV, Saccà F, et al. CD4/CD8 ratio during natalizumab treatment in multiple sclerosis patients. J Neuroimmunol. 2017;309:47–50.
30. Carruthers RL, Rotstein DL, Healy BC, Chitnis T, Weiner HL, Buckle GJ. An observational comparison of natalizumab vs. fingolimod using JCV serology to determine therapy. Mult Scler J. 2014;20:1381–90.
31. Chen Y, Bord E, Tompkins T, Miller J, Tan CS, Kinkel RP, et al. Asymptomatic reactivation of JC virus in patients treated with natalizumab. N Engl J Med. 2009;361:1067–74.
32. Clerico M, De Mercanti SF, Signori A, Iudicello M, Cordioli C, Signoriello E, et al. Extending the interval of natalizumab dosing: is efficacy preserved? Neurotherapeutics. 2020;17:200–7.
33. Cobo-Calvo A, Bau L, Matas E, Romero-Pinel L, Mañé Martínez MA, Majós C, et al. Effectiveness of natalizumab in patients with highly active relapsing remitting multiple sclerosis. Eur Neurol. 2015;73:220–9.
34. Coerver EME, Wessels MHJ, van Lierop ZYG, van Kempen ZLE, Killestein J, Strijbis EMM. Natalizumab discontinuation in a Dutch real-world cohort. Mult Scler Relat Disord [Internet]. 2021;52. https://www.embase.com/search/results?subaction=viewrecord&id=L2012002266&from=export.
35. Cohan SL, Moses H, Calkwood J, Tornatore C, LaGanke C, Smoot KE, et al. Clinical outcomes in patients with relapsing-remitting multiple sclerosis who switch from natalizumab to delayed-release dimethyl fumarate: a multicenter retrospective observational study (STRATEGY). Mult Scler Relat Disord. 2018;22:27–34.
36. Correia I, Batista S, Galego O, Marques IB, Jesus-Ribeiro J, Martins AI, et al. Long-term effectiveness and safety of natalizumab in a Portuguese population. Int Immunopharmacol. 2017;46:105–11.
37. Dale RC, Brilot F, Duffy LV, Twilt M, Waldman AT, Narula S, et al. Utility and safety of rituximab in pediatric autoimmune and inflammatory CNS disease. Neurology. 2014;83:142–50.
38. de Oliveira EML, Simm RF, Dasic G, de Morais MM, Perreira SLA, Callegaro D. Natalizumab treatment in multiple sclerosis: the experience from two Brazilian MS centers. Arq Neuropsiquiatr. 2015;73:736–40.
39. Delbue S, Elia F, Carloni C, Pecchenini V, Franciotta D, Gastaldi M, et al. JC virus urinary excretion and seroprevalence in natalizumab-treated multiple sclerosis patients. J Neurovirol. 2015;21:645–52.
40. Dominguez-Mozo MI, Rus M, Santiago JL, Izquierdo G, Casanova I, Galan V, et al. Study of the anti-JCV antibody levels in a Spanish multiple sclerosis cohort. Eur J Clin Invest. 2017;47:158–66.
41. Domínguez-Mozo MI, García-Montojo M, Arias-Leal A, García-Martínez A, Santiago JL, Casanova I, et al. Monitoring the John Cunningham virus throughout natalizumab treatment in multiple sclerosis patients. Eur J Neurol. 2016;23:182–9.
42. Foley J, Carrillo-Infante C, Smith J, Evans K, Ho P-R, Lee L, et al. The 5-year Tysabri global observational program in safety (TYGRIS) study confirms the long-term safety profile of natalizumab treatment in multiple sclerosis. Mult Scler Relat Disord [Internet]. 2020;39. https://www.embase.com/search/results?subaction=viewrecord&id=L2004476626&from=export.
43. Gajofatto A, Bianchi MR, Deotto L, Benedetti MD. Are natalizumab and fingolimod analogous second-line options for the treatment of relapsing-remitting multiple sclerosis? A clinical practice observational study. Eur Neurol. 2014;72:173–80.
44. Giacoppo S, Ruscica M, Grimaldi LM, Bramanti P, Mazzon E. The Italian pharmacovigilance program: an observational study of adverse effects of natalizumab in multiple sclerosis therapy. Med Sci Monit. 2017;23:4230–40.
45. Giannecchini S, Clausi V, Vultaggio A, Macera L, Maggi F, Martelli F, et al. Assessment of the risk of polyomavirus JC reactivation in patients with immune-mediated diseases during long-term treatment with infliximab. J Neurovirol. 2012;18:55–61.
46. the MS Study Group-Italian Society of Neurology, Ghezzi A, Moiola L, Pozzilli C, Brescia-Morra V, Gallo P, et al. Natalizumab in the pediatric MS population: results of the Italian registry. BMC Neurol. 2015;15:174.
47. Gottenberg J-E, Ravaud P, Bardin T, Cacoub P, Cantagrel A, Combe B, et al. Risk factors for severe infections in patients with rheumatoid arthritis treated with rituximab in the autoimmunity and rituximab registry. Arthritis Rheum. 2010;62:2625–32.
48. Grinyó J, Charpentier B, Pestana JM, Vanrenterghem Y, Vincenti F, Reyes-Acevedo R, et al. An integrated safety profile analysis of belatacept in kidney transplant recipients. Transplantation. 2010;90:1521–7.
49. Guger M, Enzinger C, Leutmezer F, Di Pauli F, Kraus J, Kalcher S, et al. Long-term outcome and predictors of long-term disease activity in natalizumab-treated patients with multiple sclerosis: real life data from the Austrian MS Treatment Registry. J Neurol. 2021;268:4303–10.
50. Holmén C, Piehl F, Hillert J, Fogdell-Hahn A, Lundkvist M, Karlberg E, et al. A Swedish national post-marketing surveillance study of natalizumab treatment in multiple sclerosis. Mult Scler J. 2011;17:708–19.
51. Huhn K, Bayas A, Doerck S, Frank B, Gerbershagen K, Hellwig K, et al. Alemtuzumab as rescue therapy in a cohort of 50 relapsing–remitting MS patients with breakthrough disease on fingolimod: a multi-center observational study. J Neurol. 2018;265:1521–7.
52. Jaklin AK, Benjaminsen E, Alstadhaug KB. Effectiveness of Natalizumab in Achieving No Evidence of Disease Activity (NEDA-3)—Data From a Local Norwegian Cohort. Front Neurol [Internet]. 2021;12. https://www.embase.com/search/results?subaction=viewrecord&id=L636368327&from=export.

53. Jilek S, Jaquiéry E, Hirsch HH, Lysandropoulos A, Canales M, Guignard L, et al. Immune responses to JC virus in patients with multiple sclerosis treated with natalizumab: a cross-sectional and longitudinal study. Lancet Neurol. 2010;9:264–72.
54. Karanasios P, Karachalios G, Gourgioti R, Alexopoulou A, Mastorodemos V. Patient and treatment characteristics and safety outcomes of patients with relapsing-remitting multiple sclerosis treated with natalizumab in Greece: results from the multicenter, 5-year prospective observational study 'TOPICS greece.' Mult Scler J - Exp Transl Clin [Internet]. 2021;7. https://www.embase.com/search/results?subaction=viewrecord&id=L2013322604&from=export.
55. Leurs CE, van Kempen ZLE, Dekker I, Balk LJ, Wattjes MP, Rispens T, et al. Switching natalizumab to fingolimod within 6 weeks reduces recurrence of disease activity in MS patients. Mult Scler J. 2018;24:1453–60.
56. Mancinelli CR, Scarpazza C, Cordioli C, De Rossi N, Rasia S, Turrini MV, et al. Switching to ocrelizumab in RRMS patients at risk of PML previously treated with extended interval dosing of natalizumab. Mult Scler J. 2021;27:790–4.
57. Melin A, Outteryck O, Collongues N, Zéphir H, Fleury MC, Blanc F, et al. Effect of natalizumab on clinical and radiological disease activity in a French cohort of patients with relapsing-remitting multiple sclerosis. J Neurol. 2012;259:1215–21.
58. Möhn N, Skripuletz T, Sühs K-W, Menck S, Voß E, Stangel M. Therapy with cladribine is efficient and safe in patients previously treated with natalizumab. Ther Adv Neurol Disord [Internet]. 2019;12. https://www.embase.com/search/results?subaction=viewrecord&id=L2003804109&from=export.
59. Moreira Ferreira VF, Liu Y, Healy BC, Stankiewicz JM. Effectiveness and safety of dimethyl fumarate in progressive multiple sclerosis. Mult Scler J Exp Transl Clin [Internet]. 2021;7. https://www.embase.com/search/results?subaction=vewrecord&id=L2011454383&from=export.
60. Naegelin Y, Rasenack M, Andelova M, Von Felten S, Fischer-Barnicol B, Amann M, et al. Shortening the washout to 4 weeks when switching from natalizumab to fingolimod and risk of disease reactivation in multiple sclerosis. Mult Scler Relat Disord. 2018;25:14–20.
61. Neff RT, Hurst FP, Falta EM, Bohen EM, Lentine KL, Dharnidharka VR, et al. Progressive multifocal leukoencephalopathy and use of mycophenolate mofetil after kidney transplantation. Transplantation. 2008;86:1474–8.
62. Outteryck O, Ongagna JC, Brochet B, Rumbach L, Lebrun-Frenay C, Debouverie M, et al. A prospective observational post-marketing study of natalizumab-treated multiple sclerosis patients: clinical, radiological and biological features and adverse events. The BIONAT cohort. Eur J Neurol. 2014;21:40–8.
63. Parikh A, Fox I, Leach T, Xu J, Scholz C, Patella M, et al. Long-term clinical experience with vedolizumab in patients with inflammatory bowel disease. Inflamm Bowel Dis. 2013;19:1691–9.
64. Parikh A, Stephens K, Major E, Fox I, Milch C, Sankoh S, et al. A programme for risk assessment and minimisation of progressive multifocal leukoencephalopathy developed for vedolizumab clinical trials. Drug Saf. 2018;41:807–16.
65. Patel VL, Mahévas M, Lee SY, Stasi R, Cunningham-Rundles S, Godeau B, et al. Outcomes 5 years after response to rituximab therapy in children and adults with immune thrombocytopenia. Blood. 2012;119:5989–95.
66. Pato Pato A, Costa Arpín E, Rodríguez Regal A, Rodríguez Constenla I, Cimas Hernando I, Muñoz Pousa I, et al. Progression of a series of patients with relapsing-remitting multiple sclerosis treated for 7 years with natalizumab using the "no evidence of disease activity" parameter. Neurol Engl Ed. 2020;S2173580820300055.
67. Prezioso C, Grimaldi A, Landi D, Nicoletti CG, Brazzini G, Piacentini F, et al. Risk assessment of progressive multifocal leukoencephalopathy in multiple sclerosis patients during 1 year of ocrelizumab treatment. Viruses [Internet]. 2021;13. https://www.embase.com/search/results?subaction=viewrecord&id=L2013551636&from=export.
68. Prockl V, Nickel FT, Utz KS, Fröhlich K, Engelhorn T, Hilz M-J, et al. Real world application of ocrelizumab in multiple sclerosis: single-center experience of 128 patients. J Neurol Sci [Internet]. 2020;415. https://www.embase.com/search/results?subaction=viewrecord&id=L2006757131&from=export.
69. Prosperini L, Fanelli F, Pozzilli C. Long-term assessment of No Evidence of Disease Activity with natalizumab in relapsing multiple sclerosis. J Neurol Sci. 2016;364:145–7.
70. Rauer S, Hoshi M-M, Pul R, Wahl M, Schwab M, Haas J, et al. Ocrelizumab Treatment in Patients with Primary Progressive Multiple Sclerosis: Short-term Safety Results from a Compassionate Use Programme in Germany. Clin Neurol Neurosurg [Internet]. 2020;197. https://www.embase.com/search/results?subaction=viewrecord&id=L2007750414&from=export.
71. Reboursiere E, Fouques H, Maigne G, Johnson H, Chantepie S, Gac AC, et al. Rituximab salvage therapy in adults with immune thrombocytopenia: retrospective study on efficacy and safety profiles. Int J Hematol. 2016;104:85–91.
72. Rempe T, Carlson A, Miravalle A, Gyang TV. Anti-JCV antibody index does not change during ocrelizumab-treatment. Mult Scler J - Exp Transl Clin [Internet]. 2020;6. https://www.embase.com/search/results?subaction=viewrecord&id=L2006794210&from=export.
73. Raffel J, Gafson AR, Malik O, Nicholas R. Anti-JC virus antibody titres increase over time with natalizumab treatment. Mult Scler J. 2015;21:1833–8.
74. Riancho J, Setien S, Sánchez de la Torre JR, Torres-Barquin M, Misiego M, Pérez JL, et al. Does Extended Interval Dosing Natalizumab Preserve Effectiveness in Multiple Sclerosis? A 7 Year-Retrospective Observational Study. Front Immunol [Internet]. 2021;12. https://www.embase.com/search/results?subaction=viewrecord&id=L634688715&from=export.
75. Rinaldi L, Rinaldi F, Perini P, Calabrese M, Seppi D, Grossi P, et al. No evidence of JC virus reactivation in natalizumab treated multiple sclerosis patients: an 18 month follow-up study. J Neurol Neurosurg Psychiatry. 2010;81:1345–50.
76. Rodríguez De Castro B, Barbosa CM-M, Ayastuy Ruiz A, Fernández González B. Natalizumab: safety and risk in patients with relapsing-remitting multiple sclerosis. Eur J Hosp Pharm. 2021;28:112–4.
77. Ryerson LZ, Frohman TC, Foley J, Kister I, Weinstock-Guttman B, Tornatore C, et al. Extended interval dosing of natalizumab in multiple sclerosis. J Neurol Neurosurg Psychiatry. 2016;87:885–9.
78. Ryerson LZ, Foley J, Chang I, Kister I, Cutter G, Metzger RR, et al. Risk of natalizumab-associated PML in patients with MS is reduced with extended interval dosing. Neurology. 2019. https://doi.org/10.1212/WNL.0000000000008243.
79. Saida T, Yokoyama K, Sato R, Makioka H, Iizuka Y, Hase M, et al. Safety and effectiveness of natalizumab: first report of interim results of post-marketing surveillance in Japan. Neurol Ther. 2017;6:197–211.
80. Salzer J, Svenningsson R, Alping P, Novakova L, Björck A, Fink K, et al. Rituximab in multiple sclerosis: a retrospective observational study on safety and efficacy. Neurology. 2016;87:2074–81.
81. Sarsour K, Beckley-Kartey S, Melega S, Odueyungbo A, Kirchner P, Khalife N, et al. Rituximab utilization for approved and off-label nononcology indications and patients' experiences with the Patient Alert Card. Pharmacol Res Perspect [Internet].

2020;8. https://www.embase.com/search/results?subaction=viewrecord&id=L2004234705&from=export.
82. Singh N, Deshpande R, Rabizadeh S, Dubinsky M. Real world experience with Natalizumab at a tertiary care pediatric IBD center. J Pediatr Gastroenterol Nutr. 2016;62:863–6.
83. Sousa L, de Sa J, Sa MJ, Cerqueira JJ, Martins-Silva A, Portugal Experience with Natalizumab Study Group. The efficacy and safety of natalizumab for the treatment of multiple sclerosis in Portugal: a retrospective study. Rev Neurol. 2014;59:399–406.
84. Tanaka M, Kinoshita M, Tomita Y, Tanaka K. CD4+CD62L+ cells: a monitoring marker of fingolimod dosage in multiple sclerosis. Clin Exp Neuroimmunol. 2020;11:26–32.
85. Trampe AK, Hemmelmann C, Stroet A, Haghikia A, Hellwig K, Wiendl H, et al. Anti-JC virus antibodies in a large German natalizumab-treated multiple sclerosis cohort. Neurology. 2012;78:1736–42.
86. Uleri E, Ibba G, Piu C, Caocci M, Serra C, Dolei A. JC polyomavirus expression and bell-shaped regulation of its SF2/ASF suppressor in multiple sclerosis patients under therapy with Natalizumab. J Neurovirol. 2016;22:S77–8.
87. van Lierop ZYGJ, Toorop AA, Coerver EME, Willemse EAJ, Strijbis EMM, Kalkers NF, et al. Ocrelizumab after natalizumab in JC-virus positive relapsing remitting multiple sclerosis patients. Mult Scler J - Exp Transl Clin [Internet]. 2021;7. https://www.embase.com/search/results?subaction=viewrecord&id=L2012309811&from=export.
88. van Pesch V, Bartholomé E, Bissay V, Bouquiaux O, Bureau M, Caekebeke J, et al. Safety and efficacy of natalizumab in Belgian multiple sclerosis patients: subgroup analysis of the natalizumab observational program. Acta Neurol Belg. 2014;114:167–78.
89. Vennegoor A, Van Rossum JA, Polman CH, Wattjes MP, Killestein J. Longitudinal JCV serology in multiple sclerosis patients preceding natalizumab-associated progressive multifocal leukoencephalopathy. Mult Scler J. 2015;21:1600–3.
90. Vukusic S, Rollot F, Casey R, Pique J, Marignier R, Mathey G, et al. Progressive multifocal leukoencephalopathy incidence and risk stratification among natalizumab users in France. JAMA Neurol. 2020;77:94–102.
91. Yamout BI, El-Ayoubi NK, Nicolas J, Kouzi YE, Khoury SJ, Zeineddine MM. Safety and efficacy of rituximab in multiple sclerosis: A retrospective observational study. J Immunol Res [Internet]. 2018;2018. https://www.embase.com/search/results?subaction=viewrecord&id=L626713562&from=export.
92. Zanghì A, Gallo A, Avolio C, Capuano R, Lucchini M, Petracca M, et al. Exit strategies in natalizumab-treated RRMS at high risk of progressive multifocal leukoencephalopathy: a multicentre comparison study. Neurotherapeutics. 2021;18:1166–74.
93. Ziemssen T, Lang M, Tackenberg B, Schmidt S, Albrecht H, Klotz L, et al. Long-term real-world evidence for sustained clinical benefits of fingolimod following switch from natalizumab. Mult Scler Relat Disord [Internet]. 2020;39. https://www.embase.com/search/results?subaction=viewrecord&id=L2004306295&from=export.
94. Zivadinov R, Dwyer M, Hussein S, Carl E, Kennedy C, Andrews M, et al. Voxel-wise magnetization transfer imaging study of effects of natalizumab and IFNβ-1a in multiple sclerosis. Mult Scler J. 2012;18:1125–34.
95. Clerico M, Schiavetti I, De Mercanti SF, Piazza F, Gned D, Brescia Morra V, et al. Treatment of relapsing-remitting multiple sclerosis after 24 doses of natalizumab: evidence from an italian spontaneous, prospective, and observational study (the TY-STOP Study). JAMA Neurol. 2014;71:954.
96. Albano L, Banas B, Klempnauer JL, Glyda M, Viklicky O, Kamar N. OSAKA trial: a randomized, controlled trial comparing tacrolimus QD and BD in kidney transplantation. Transplantation. 2013;96:897–903.
97. Confavreux C, Li DK, Freedman MS, Truffinet P, Benzerdjeb H, Wang D, et al. Long-term follow-up of a phase 2 study of oral teriflunomide in relapsing multiple sclerosis: safety and efficacy results up to 8.5 years. Mult Scler J. 2012;18:1278–89.
98. Feagan BG, Greenberg GR, Wild G, Fedorak RN, Paré P, McDonald JWD, et al. Treatment of active Crohn's disease with MLN0002, a humanized antibody to the α4β7 integrin. Clin Gastroenterol Hepatol. 2008;6:1370–7.
99. Giovannoni G, Wiendl H, Turner B, Umans K, Mokliatchouk O, Castro-Borrero W, et al. Circulating lymphocyte levels and relationship with infection status in patients with relapsing–remitting multiple sclerosis treated with daclizumab beta. Mult Scler J. 2018;24:1725–36.
100. Hibi T, Motoya S, Ashida T, Sai S, Sameshima Y, Nakamura S, et al. Efficacy and safety of abrilumab, an α4β7 integrin inhibitor, in Japanese patients with moderate-to-severe ulcerative colitis: a phase II study. Intest Res. 2019;17:375–86.
101. Klintmalm GB, Feng S, Lake JR, Vargas HE, Wekerle T, Agnes S, et al. Belatacept-based immunosuppression in de novo liver transplant recipients: 1-year experience from a phase II randomized study. Am J Transpl. 2014;14:1817–27.
102. Mehta D, Miller C, Arnold DL, Bame E, Bar-Or A, Gold R, et al. Effect of dimethyl fumarate on lymphocytes in RRMS: implications for clinical practice. Neurology. 2019;92:e1724–38.
103. Miller DH, Weber T, Grove R, Wardell C, Horrigan J, Graff O, et al. Firategrast for relapsing remitting multiple sclerosis: a phase 2, randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2012;11:131–9.
104. Ng SC, Hilmi IN, Blake A, Bhayat F, Adsul S, Khan QR, et al. Low frequency of opportunistic infections in patients receiving vedolizumab in clinical trials and post-marketing setting. Inflamm Bowel Dis. 2018;24:2431–41.
105. Pescovitz MD, Greenbaum CJ, Krause-Steinrauf H, Becker DJ, Gitelman SE, Goland R, et al. Rituximab, B-lymphocyte depletion, and preservation of beta-cell function. N Engl J Med. 2009;361:2143–52.
106. Reinisch W, Sandborn WJ, Danese S, Hébuterne X, Kłopocka M, Tarabar D, et al. Long-term safety and efficacy of the anti-MAdCAM-1 monoclonal antibody ontamalimab [SHP647] for the treatment of ulcerative colitis: the open-label study TURANDOT II. J Crohns Colitis. 2021;15:938–49.
107. Rigby W, Tony H-P, Oelke K, Combe B, Laster A, von Muhlen CA, et al. Safety and efficacy of ocrelizumab in patients with rheumatoid arthritis and an inadequate response to methotrexate: Results of a forty-eight-week randomized, double-blind, placebo-controlled, parallel-group phase III trial. Arthritis Rheum. 2012;64:350–9.
108. Rudick RA, Stuart WH, Calabresi PA, Confavreux C, Galetta SL, Radue E-W, et al. Natalizumab plus interferon Beta-1a for relapsing multiple sclerosis. N Engl J Med. 2006;354:911–23.
109. Saida T, Kira J-I, Kishida S, Yamamura T, Ohtsuka N, Ling Y, et al. Safety and efficacy of natalizumab in Japanese patients with relapsing-remitting multiple sclerosis: open-label extension study of a phase 2 trial. Neurol Ther. 2017;6:39–55.
110. Sandborn WJ, Colombel JF, Enns R, Feagan BG, Hanauer SB, Lawrance IC, et al. Natalizumab induction and maintenance therapy for Crohn's disease. N Engl J Med. 2005;353:1912–25.
111. Sandborn WJ, Cyrille M, Hansen MB, Feagan BG, Loftus EV, Rogler G, et al. Efficacy and safety of abrilumab in a randomized, placebo-controlled trial for moderate-to-severe ulcerative colitis. Gastroenterology. 2019;156:946-957.e18.
112. Sands BE, Feagan BG, Rutgeerts P, Colombel J-F, Sandborn WJ, Sy R, et al. Effects of vedolizumab induction therapy for patients

with Crohn's disease in whom tumor necrosis factor antagonist treatment failed. Gastroenterology. 2014;147:618-627.e3.
113. Schiopu E, Chatterjee S, Hsu V, Flor A, Cimbora D, Patra K, et al. Safety and tolerability of an anti-CD19 monoclonal antibody, MEDI-551, in subjects with systemic sclerosis: a phase I, randomized, placebo-controlled, escalating single-dose study. Arthritis Res Ther. 2016;18:131.
114. Tak PP, Rigby WF, Rubbert-Roth A, Peterfy CG, van Vollenhoven RF, Stohl W, et al. Inhibition of joint damage and improved clinical outcomes with rituximab plus methotrexate in early active rheumatoid arthritis: the IMAGE trial. Ann Rheum Dis. 2011;70:39–46.
115. Targan SR, Feagan BG, Fedorak RN, Lashner BA, Panaccione R, Present DH, et al. Natalizumab for the treatment of active Crohn's disease: results of the ENCORE trial. Gastroenterology. 2007;132:1672–83.
116. van Kempen ZLE, Hoogervorst ELJ, Wattjes MP, Kalkers NF, Mostert JP, Lissenberg-Witte BI, et al. Personalized extended interval dosing of natalizumab in MS: a prospective multicenter trial. Neurology. 2020;95:e745–54.
117. Vo AA, Lukovsky M, Toyoda M, Wang J, Reinsmoen NL, Lai C-H, et al. Rituximab and intravenous immune globulin for desensitization during renal transplantation. N Engl J Med. 2008;359:242–51.
118. Wallace DJ, Ginzler EM, Merrill JT, Furie RA, Stohl W, Chatham WW, et al. Safety and efficacy of belimumab plus standard therapy for up to thirteen years in patients with systemic lupus erythematosus. Arthritis Rheumatol. 2019;71:1125–34.
119. Wang Y, Marier J, Lavigne J, Kassir N, Martin P. Population pharmacokinetics and pharmacodynamics of ontamalimab (SHP647), a fully human monoclonal antibody against mucosal addressin cell adhesion molecule-1 (MAdCAM-1), in patients with ulcerative colitis or Crohn's disease. J Clin Pharmacol. 2020;60:903–14.
120. Foley JF, Defer G, Ryerson LZ, Cohen JA, Arnold DL, Butzkueven H, et al. Comparison of switching to 6-week dosing of natalizumab versus continuing with 4-week dosing in patients with relapsing-remitting multiple sclerosis (NOVA): a randomised, controlled, open-label, phase 3b trial. Lancet Neurol [Internet]. 2022; https://www.embase.com/search/results?subaction=viewrecord&id=L637900723&from=export. Accessed 5 Dec 2022.
121. Berger JR, Cree BA, Greenberg B, Hemmer B, Ward BJ, Dong VM, et al. Progressive multifocal leukoencephalopathy after fingolimod treatment. Neurology. 2018;90:E1815–21.
122. Bianchi A, Ragonese P, Banco MA, Realmuto S, Vazzoler G, Portera E, et al. Four cases of progressive multifocal leukoencephalopathy in iatrogenic immunocompromised patients. eNeurologicalSci. 2020;19:100243.
123. Patel A, Sul J, Gordon ML, Steinklein J, Sanguinetti S, Pramanik B, et al. Progressive multifocal leukoencephalopathy in a patient with progressive multiple sclerosis treated with ocrelizumab monotherapy. JAMA Neurol. 2021;78:736–40.
124. FDA. Food and Drug Administration, US UPLIZNA Product Information. [Internet]. 2023 Sep. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761142s000lbl.pdf.
125. Husseini L, Leussink VI, Kieseier BC, Hartung H-P. 4-Aminopyridin (fampridin): ein neuer ansatz zur symptomatischen therapie der multiplen sklerose. Nervenarzt. 2010;81:203–11.
126. Mahurkar S, Suppiah V, O'Doherty C. Pharmacogenomics of interferon beta and glatiramer acetate response: a review of the literature. Autoimmun Rev. 2014;13:178–86.
127. Jordan ALM, Yang J, Fisher CJ, Racke MK, Mao-Draayer Y. Progressive multifocal leukoencephalopathy in dimethyl fumarate-treated multiple sclerosis patients. Mult Scler J. 2022;28:7–15.
128. Food and Drug Administration Adverse Event Reporting System (FAERS - Public Dashboard). Food and Drug Administration Adverse Event Reporting System (FAERS - Public Dashboard) - [Internet]. https://fis.fda.gov/sense/app/95239e26-e0be-42d9-a960-9a5f7f1c25ee/sheet/8eef7d83-7945-4091-b349-e5c41ed49f99/state/analysis. Accessed on 10 Sep 2023.
129. McEntire CRS, Fletcher A, Toledano M, Epstein S, White E, Tan CS, et al. Characteristics of progressive multifocal leukoencephal pathy associated with sarcoidosis without therapeutic immune suppression. JAMA Neurol. 2023;80:624.
130. Bozic C, Subramanyam M, Richman S, Plavina T, Zhang A, Ticho B. Anti-JC virus (JCV) antibody prevalence in the JCV Epidemiology in MS (JEMS) trial. Eur J Neurol. 2014;21:299–304.
131. Page MJ, Sterne JAC, Higgins JPT, Egger M. Investigating and dealing with publication bias and other reporting biases in meta-analyses of health research: a review. Res Synth Methods. 2021;12:248–59.

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