Review Article

The Prevalence of Cancer in Patients with Multiple Sclerosis (MS) who were Under Treatment with Natalizumab (Tysabri): A Systematic Review and Meta-Analysis

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Abstract

Background: To determine the pooled prevalence of cancer in subjects with multiple sclerosis (MS) who received Natalizumab. **Methods:** Two researchers systematically searched PubMed, Scopus, EMBASE, Web of Science, google scholar, and gray literature including references of the included studies. The search strategy which was used in PubMed was ("Disseminated Sclerosis" OR "multiple sclerosis" OR "MS" OR "Acute Fulminating") AND ("Cancer" OR "Neoplasia*" OR "Neoplasm*" OR "Tumor*" OR "Malignancy" OR "Benign Neoplasm" OR "Malignant neoplasm") AND ("Tysabri" OR "Antegren" OR "natalizumab" OR "Modifying Therapy"). **Results:** We found 1,993 articles by literature search, and 1,573 studies remained after removing duplicate studies. For metaanalysis, we used the extracted data of eight studies. The pooled prevalence of cancer in patients who received Natalizumab was 2% (95%CI: 1–3%; I^2: 99.4%, $P < 0.001$). The pooled prevalence of basal cell carcinoma in patients with cancer was 12% (95%CI: 5–20%; I^2:50.3%, $P = 0.13$). **Conclusions:** The main finding of this systematic review and metaanalysis is that the pooled prevalence of cancer in subjects who suffer from MS and received natalizumab was 2%.

Keywords: *Multiple sclerosis, neoplasm, prevalence*

Introduction

Multiple sclerosis (MS) is an inflammatory, autoimmune disease of central nervous system (CNS) that affects youth all over the world.[1] The most common form of the disease is relapsing-remitting (RR) that accounts for nearly 85% of all MS types.[2] Interferon-beta and glatiramer acetate are the first disease-modifying therapies for patients with MS while their effectiveness is not high.[3] Natalizumab is a monoclonal antibody, an a4-integrin antagonist, is a disease-modifying therapy (DMT) which is administered in subjects with MS.[4] Natalizumab prevents migration of lymphocytes across the blood–brain barrier.[4] It is widely used for treating RR form of MS disease.[5,6] Its safety and efficacy profile is acceptable while concern regarding developing progressive multifocal leukoencephalopathy (PML) raises during treatment with this medication.[7]

Subjects with MS have higher rate of mortality compared with their age- and sex-matched controls due to secondary complications of MS.[8,9] Infectious, respiratory, and cardiovascular diseases as well as malignancies are the most frequent leading causes of death in individuals with MS.[10,11]

Smoking, vitamin D deficiency, and genetics are among common etiological factors between cancers and MS.[12]

Previous studies reported different rates of cancer in MS patients who are under treatment with various medications such as Natalizumab.

So, we designed this systematic review and meta-analysis to estimate the pooled prevalence of cancer in MS patients who received Natalizumab.

Methods

The protocol of this systematic review was approved in Tehran University of medical sciences (IR.TUMS.NI.REC.1400.053).

The search terms were:

We systematically and comprehensively searched PubMed, Scopus, EMBASE, Web of Science, google scholar, and gray

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literature including references of the included studies that were published before October 2021.

("Disseminated Sclerosis" OR "multiple sclerosis" OR "MS" OR "Acute Fulminating") AND ("Cancer" OR "Neoplasia*" OR "Neoplasm*" OR "Tumor*" OR "Malignancy" OR "Benign Neoplasm" OR "Malignant neoplasm") AND ("Tysabri" OR "Antegren" OR "natalizumab" OR "Modifying Therapy").

We included studies if their design was cohort and providing information regarding the number of included patients who were treated with Natalizumab and incident number of cancer and also studies which were published in English language.

We excluded studies which were case-control, cross-sectional studies, and case reports.

Data extraction

Two researchers extracted data regarding the total number of patients, first author name, publication year, country of origin, and number of patients with cancer from the included studies.

If discrepancies were found, the third one reviewed the forms.

Risk of bias assessment

We assessed the potential risk of bias in included studies was evaluated using the Hoy assessment scale.[13]

Statistical analysis

We conducted statistical analyses were performed using STATA (Version 13.0; Stata Corp LP, College Station, TX, USA). We used the inverse variance with random effects model. To determine heterogeneity, Inconsistency (I2) was calculated.

Results

We found 1,993 articles by literature search, and after deleting duplicates 1,573 remained. Eight articles remained for metaanalysis [Figure 1].

Eight articles were included. The basic characteristics of the included studies [Table 1].

The pooled prevalence of cancer in patients who received Natalizumab was 2% (95%CI: 1–3%; I^2:99.4%, $P < 0.001$) [Figure 2].

The pooled prevalence of basal cell carcinoma in patients with cancer was 12% (95%CI: 5–20%; I^2:50.3%, $P = 0.13$) [Figure 3].

The quality assessment of included studies are reported in Table 2.

Discussion

To the best of our knowledge, this is the first study

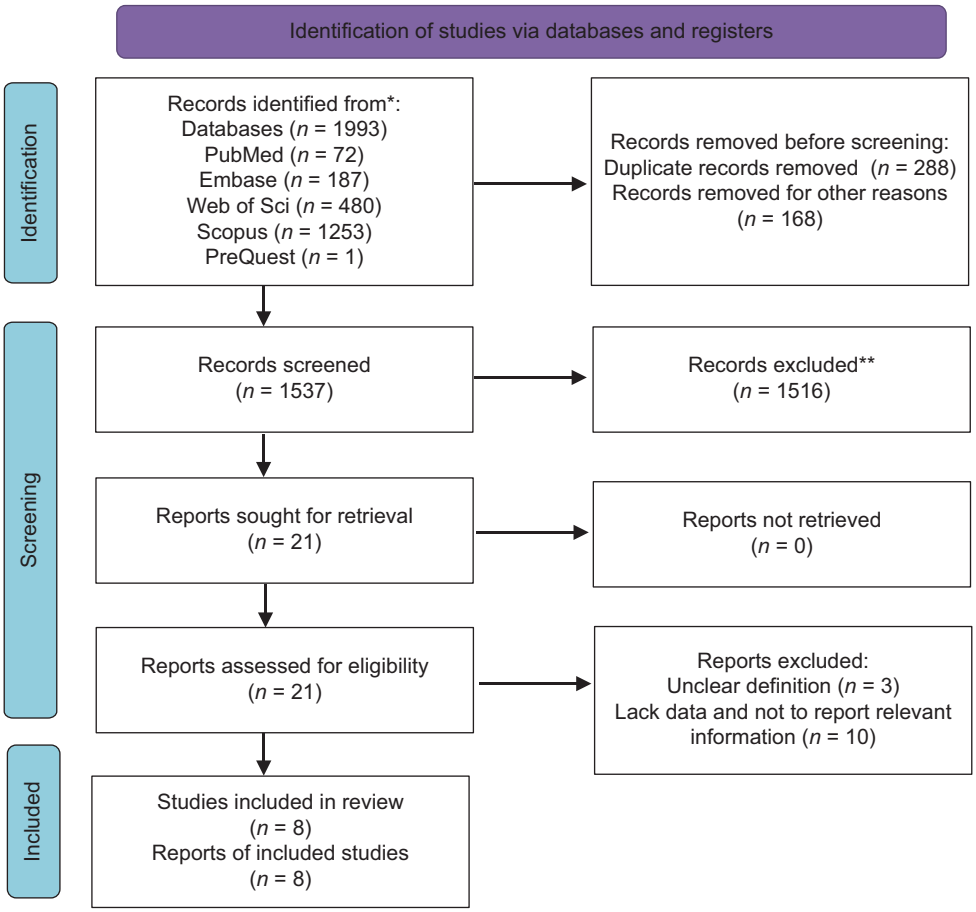

Figure 1: Flow diagram summarizing the selection of eligible studies

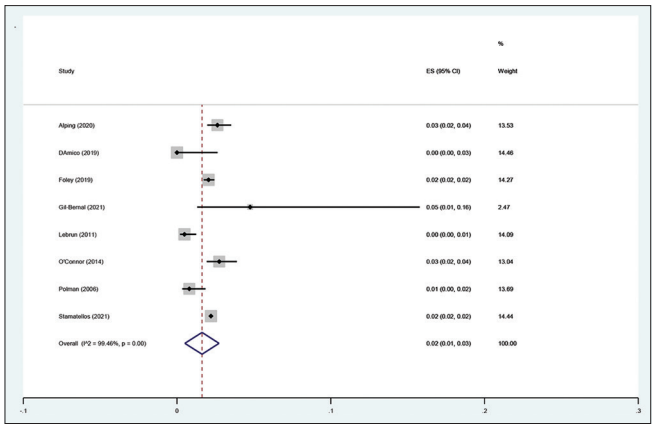

Figure 2: The pooled prevalence of basal cell carcinoma in cases who received Natalizumab

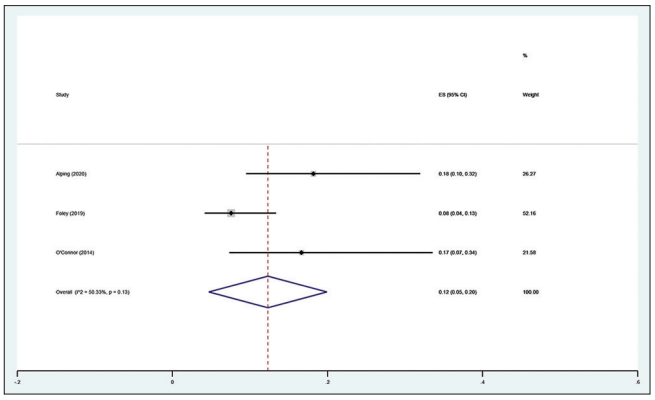

Figure 3: The pooled prevalence of basal cell carcinoma in patients with cancer

evaluating the pooled prevalence of cancer in MS cases who received natalizumab. The results show that the pooled prevalence is 2% ranging from 0 to 5%. This finding could show that cancers should be evaluated in subjects with MS who receive Natalizumab. As it was mentioned in the introduction, MS is not a fatal disease and most cases die due to complications such as infections, respiratory diseases, and cancers.[10,11]

Recent innovation by disease modifying therapies such as Natalizumab has lead to better clinical progress, and quality of life improvement.[14] Better antiinflammatory responses and neuroprotective effects are advantages of Natalizumab treatment,[14] but hepatotoxicity, allergic reactions, progressive multifocal leukoencephalopathy (PML) development, and a higher risk of infection are among disadvantages of Natalizumab treatment.[15]

Previous studies showed risk of developing cancer in subjects who received Natalizumab is not higher.[4,16]

Basal cell carcinoma was reported by most studies and its pooled prevalence was12%.

In general population, breast, colorectal, prostate, lung, and stomach cancers are the most frequent neoplasm, and breast, cervical, and thyroid are the most common cancers in women.[17] In MS cases, the most incident cancers reported as breast, and digestive cancers.[12]

Foley *et al*.[18] enrolled 6,634 MS patients who received natalizumab and reported malignant incidence as 449.0 per 100,000 patient-years. The most prevalent cancers among women and men in their study were breast and colon cancers, respectively.

In another large safety study, Stamatellos *et al*.[19] enrolled 56,767 MS patients who were under treatment with natalizumab and reported cancer in 2.3%.

In another study, Polman *et al*.[20] included 627 MS cases who were treated by natalizumab and found malignancies in 5.

Natalizumab is effective in patients with RR type of the disease while has multifocal leukoencephalopathy (PML) as its complication.[6] PML is life threatening, so monitoring of JCV antibody status is necessary for patients who administer this medication.

Natalizumab is a monoclonal antibody which is approved for treating RR form of MS which slows down the progression of symptoms and decreases the rate of flare up.[21] It decreases inflammation by blocking the cross of leukocytes from the blood vessel which leads to inflammation decrease.[21]

It is shown that natalizumab plays role in rapid progression of the CNS diffuse large B-cell lymphomas (CNSL)[16] and also some modifications in pigmented lesions.[22] The incidence of melanoma in cases who received natalizumab estimated as 5/100,000 MS person-years.[22]

Overall, it seems that administration of natalizumab is not related with higher risk of cancer in subjects with MS.

This systematic review has some limitation. First, all studies did not report the prevalence of each neoplasm separately. Second, the number of included studies was limited. Third, there was no exact data regarding the time between the availability and affordability of the drug and the incidence of cancers.

Conclusions

The main finding of this systematic review and metaanalysis is that the pooled prevalence of cancer in subjects who suffer from MS and received natalizumab was 2%.

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Conflicts of interest

There are no conflicts of interest.

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Table 1: Basic characteristics of included studies

Table X. Characteristics of included studies.

Author	Year	Country	Female	Male	Total sample MS	Patient cancer	Use natalizumab	NTB cancer	BCC	LTC	OCPC	SCC	UN/NM	FBC	BC	CC	MM	CIN
Alping	2020	Sweden	5287	849	6136	204	1670	44	8				17	2			2	15
DAmico	2019	Italy	792	388	1180	36	142	0										
Foley	2019	Multi-country	4749	1759	6434	132	6434	132	10	4	5	7	64		33		9	
Gil-Bernal	2021	Spain	158	92	250	66	42	2					2					
Lebrun	2011	France	15220	5773	20993	189	820	4					4					
O'Connor	2014	Canada	755	339	1094	30	1094	30	5				25					
Polman	2006	Multi-country	660	282	942	6	627	5						3		1	1	
Stamatellos	2021	Greece	129029	35529	164558	6259	56767	1257					1257					

BCC: Basal cell carcinoma; LTC: leukemia (various types) and thyroid cancers; OCPC: Oral cavity and pharynx cancers; SCC: Squamous cell carcinoma; UN/NM: Unspecified Neoplasm/Not mentioned; FBC: Female breast cancer; BC: Breast cancer (male and female); CC: Cervical cancer; MM: Metastatic melanoma; CIN: Cervical Intraepithelial Neoplasia

Table 2: Quality assessment of included studies

Table X. Quality assessment checklist for included studies

Author	Was the study's target population a close representation of the national population in relation to relevant variables, e.g., age, sex, occupation?	Was the sampling frame a true or close representation of the target population?	Was some form of random selection used to select the sample, OR, was a census undertaken?	Was the likelihood of non-response bias minimal?	Were data collected directly from the subjects (as opposed to a proxy)?	Was an acceptable case definition used in the study?	Was the study instrument that measured the parameter of interest (e.g., prevalence of low back pain) shown to have reliability and validity (if necessary)?	Was the same mode of data collection used for all subjects?	Were the numerator (s) and denominator (s) for the parameter of interest appropriate	Summary on the overall risk of study bias	Total score
Alping	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	1
DAmico	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	0
Foley	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	2
Gil-Bernal	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	0
Lebrun	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	0
O'Connor	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	1
Polman	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	1
Stamatellos	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	0

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