Alopecia in Multiple Sclerosis Patients Treated with Disease Modifying Therapies

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ABSTRACT

BACKGROUND: There is currently limited literature addressing the reporting of alopecia in multiple sclerosis (MS) patients treated with disease-modifying therapies (DMTs). Anecdotal reports of hair thinning from patients on various DMTs prompted further investigation of a large database.

OBJECTIVE: To analyze total reports, source of reporting, age distribution, and sex distribution of alopecia associated with DMTs.

METHODS: FDA Adverse Event Reporting System (FAERS) public dashboard and OpenFDA database were analyzed for alopecia reports between January 1, 2009, and June 30, 2020, attributed to usage in MS of FDA approved DMTs. The main outcomes included total reports for each drug, age, sex distribution, and reporting source. OpenFDA data was used for statistical analyses including reporting odds ratios (ROR) and information components.

RESULTS: 8759 alopecia reports were identified among 44 114 adverse events in skin and subcutaneous tissue disorders (19.9%). 3701 (42.3%) with teriflunomide, 1675 (19.1%) with dimethyl fumarate, 985 (11.2%) with natalizumab, 926 (10.6%) with fingolimod, 659 (7.5%) with interferon beta-1a, 257 (2.9%) with glatiramer acetate, 243 (2.8%) with ocrelizumab, 124 (1.4%) with interferon beta-1b, 117 (1.3%) with alemtuzumab, 36 (.4%) with siponimod, 24 (.3%) with cladribine, and 12 (.1%) with rituximab. Reports were mostly made by patients (78.3%) and highest in fifth and sixth decades of life. OpenFDA analyses showed increased ROR (ROR 95% confidence interval) of alopecia in females with teriflunomide (18.00, 17.12-18.93), alemtuzumab (1.43, 1.16-1.76), dimethyl fumarate (1.26, 1.18-1.34), and ocrelizumab (1.28, 1.11-1.49). Increased ROR in males was associated with teriflunomide (24.65, 20.72-29.31).

CONCLUSION: We identified many reports of alopecia for DMTs in addition to teriflunomide. Within the limitations of the database, increased RORs of alopecia were observed for females treated with alemtuzumab, dimethyl fumarate, and ocrelizumab. The source of reporting was largely driven by female patients. Possible alopecia, even if transient, should be considered during patient education when starting DMTs.

KEYWORDS: Multiple sclerosis, alopecia, hair loss, disease modifying therapy

Introduction

Multiple sclerosis (MS) is a neurodegenerative, inflammatory, and demyelinating central nervous system disease.[1] Disease-modifying therapy (DMT) refers to various medication classes with different mechanisms of action aiming to reduce relapse rates, MRI activity, and slow disease progression. DMTs have distinct safety profiles and variable adverse effects.[2] These are often discussed with MS patients before treatment initiation to allow for informed decision-making under the guidance of the neurologist.

Alopecia, or inappropriate hair loss, is defined as incomplete or complete hair loss from areas of the body where it usually grows.[3] The 2 broad classifications of hair loss consist of scarring and nonscarring forms. Scarring alopecia is generally irreversible due to destruction of stem cells while the more common, nonscarring forms may have potential for regrowth.[4] Out of an average of 100 000 scalp hairs, more than 90% are in an actively growing stage called anagen.[5] After anagen, hairs enter an apoptotic catagen phase, followed by a resting telogen phase before falling out. Approximately 100 hairs are lost on the scalp each day through this normal physiological hair cycle.[5] However, increased hair loss due to androgenic and genetic factors, known as androgenic alopecia, affects up to 80% of men and

50% of women during their lifetime,[6] with risks increasing with age.[7] Additionally, up to 2% of the general population will be affected into several forms of immunological alopecia such as alopecia areata.[8] While debate exists regarding age and other demographic differences for alopecia areata, the prevalence is increasing over time and is greater in younger individuals.[8]

Hair loss is a possible side effect that is classically linked to teriflunomide or the class of interferons.[9-11] Hair loss or alopecia can cause profound personal impacts and can be a source of significant psychological concern for some patients.[3] While the prescribing label for teriflunomide and interferons guide the treating neurologist to discuss hair loss as a possible side effect (often is transient), there is no guidance on whether to discuss the potential for this side effect with patients initiating other DMTs. Subsequently, we performed a literature search and identified a gap of knowledge regarding hair loss associated with various DMTs from the patient perspective, with data only stemming from scarce case reports. Thus, we aimed to examine alopecia reports associated with the use of various DMTs utilizing the FDA Adverse Event Reporting System (FAERS) and OpenFDA database. These reports are voluntarily submitted to the FDA by patients and healthcare professionals, which are deidentified and accessible to the general public.[12] The goal of this study was to analyze the number of reports and proportions/odds of reported alopecia (hair thinning) per medication and acknowledge patient perspective into this important underrecognized topic. Thus, we aimed to stratify the reports based on age, biological sex, and report source.

Methods

The study is a retrospective study of the FDA Adverse Event Reporting System (FAERS), a self-reported medication adverse event database that includes post-marketing adverse reports.[12] In this database, the adverse events for drugs are categorized by reaction terms. We queried the public dashboard for yearly reported alopecia cases for each drug between January 1, 2009, and June 30, 2020 (determined by "Initial FDA Received Date") using the reaction term "alopecia", classified under "Skin and Subcutaneous Tissue Disorders" for ocrelizumab, interferon beta-1a, interferon beta-1b, glatiramer acetate, dimethyl fumarate, fingolimod, teriflunomide, alemtuzumab, natalizumab, cladribine, siponimod, and rituximab. By utilizing the general keyword "alopecia", all reaction terms containing the word alopecia were collected in order to capture different variants. In attempts to decrease disease-related bias, we excluded reports where the reason for use did not contain the keyword "Multiple Sclerosis", which includes all other forms of MS. However, it should be noted that this could mask other potential signals by decreasing recorded reports. Additionally, we excluded ozanimod due to no alopecia reports, likely due to recent approval in March 2020.

Statistical Analysis

We calculated the overall and proportional reports and represented the data graphically using bar charts. Cases were stratified by age group, sex, and report source. Further analyses were conducted using the OpenFDA application programming interface system. This system was utilized in addition to the FAERS public dashboard since it allows for greater accessibility of data to perform statistical analyses such as reporting odds ratios (ROR) and information components (IC), frequentist and Bayesian methods, respectively, which represent the standard practice for quantitative analyses of data in FAERS and similar spontaneous reporting databases.[13,14] It is important to note that differences exist in data between the FAERS public dashboard and OpenFDA because OpenFDA data undergoes a harmonization process which requires an exact match of fields. Therefore, OpenFDA data is generally more restricted since reports that did not match during the data harmonization process are not included. Reports were selected if the included the term, "Multiple Sclerosis", as drug indication; "[drug.-drugindication]". The date was filtered by the date the report was initially received "[receiptdate]". The results were further filtered out by a unique case variable, "[safetyreportid.exact]", to avoid duplicates. The process was repeated but with "alopecia" as an adverse event variable "[reaction.reactionmeddrapt]". The selection was repeated for each multiple sclerosis drug we studied using the generic name in the variable "[drug.activesubstance]". ROR represents the odds that alopecia is reported in MS patients who take the specific drug of interest compared to all other patients in the database who take other drugs. We calculated the ROR for each drug using the formula $(a/c)/(b/d)$ and the standard formula for confidence intervals where "a" indicated alopecia occurrence, "b" as drug adverse events other than alopecia for the drug of interest. For the reports of all drugs in the database, without the drug of interest, we defined the number of alopecia reports as "c" and all other adverse event reports as "d". The process was repeated separately for male patients and female patients. The IC and lower limit of its 95% credible interval (IC025) were calculated for each drug to measure the disproportionality between the observed and expected number of drug-adverse event combination. The calculations for IC and IC025 were performed using previously published pharmacovigilance methods.[15] The IC indicates how many excess reports of alopecia were reported for the drug of interest relative to what would be expected if the drug and reported alopecia were independent of 1 another. The significance level for ROR was determined using a 95% confidence interval and significance of IC was determined by an IC025 greater than zero.[15]

Standard Protocol Approvals, Registrations, and Patient Consents

The Medical College of Wisconsin and Froedtert hospital Institutional Review Board determined that the project does not meet criteria for human subject research under protocol number 36447.

Table 1. Alopecia reports, mean age, and female to male ratios between Jan 1, 2009 and June 30, 2020.

DRUG	TOTAL ALOPECIA REPORTS (JAN 1 2009-JUNE 30, 2020)	MEAN AGE ± SD[a]	PROPORTION OF FEMALE REPORTS[b]
Teriflunomide	3701	50.58 ± 11.04	.8621
Dimethyl fumarate	1675	48.33 ± 12.10	.8860
Natalizumab	985	45.40 ± 11.75	.9228
Fingolimod	926	43.19 ± 12.27	.9352
Interferon Beta-1a	659	46.99 ± 12.45	.9196
Glatiramer acetate	257	44.95 ± 13.73	.8677
Ocrelizumab	243	46.95 ± 11.87	.9259
Interferon Beta-1b	124	44.90 ± 13.21	.9355
Alemtuzumab	117	40.04 ± 10.46	.8376
Siponimod	36	46.08 ± 10.84	.8056
Cladribine	24	40.88 ± 9.05	.7083
Rituximab	12	47.20 ± 8.30	.8333

[a]Age not specified by 765 for teriflunomide, 733 for dimethyl fumarate, 372 for fingolimod 289 for natalizumab, 207 for interferon beta-1a, 137 for glatiramer acetate, 73 for ocrelizumab, 31 for interferon beta-1b, 14 for alemtuzumab, 10 for siponimod, 8 for cladribine, and 7 for rituximab.
[b]Sex not specified by 230 for teriflunomide, 113 for dimethyl fumarate, 19 for natalizumab, 13 for fingolimod, 12 for interferon beta-1a, 20 for glatiramer acetate, 7 for ocrelizumab, 11 for alemtuzumab, 5 for cladribine, 5 for siponimod and 2 for rituximab.

Data Availability

The data collected in this study are publicly available via FAERS and OpenFDA websites. Compiled raw data and analyses conducted in our study are available to any qualified author upon request.

Results

A total of 8759 reports of alopecia among 44 114 adverse event reports in the skin and subcutaneous tissue disorders (19.9%) were identified in MS patients. Of those, there were 3701 (42.3%) with teriflunomide, 1675 (19.1%) with dimethyl fumarate, 985 (11.2%) with natalizumab, 926 (10.6%) with fingolimod, 659 (7.5%) with interferon beta-1a, 257 (2.9%) with glatiramer acetate, 243 (2.8%) with ocrelizumab, 124 (1.4%) with interferon beta-1b, 117 (1.3%) with alemtuzumab, 36 (.4%) with siponimod, 24 (.3%) with cladribine, and 12 (.1%) with rituximab. Table 1 shows the total number of alopecia reports, mean age (SD), and proportion of reports by females per DMT. Figure 1 shows the percent of alopecia reports out of all reports of skin and subcutaneous tissue disorders for each DMT. Reports for teriflunomide were disproportionally high. The proportion of reports by female patients largely outnumbered those by male patients. There were 91 alopecia reports for ocrelizumab in 2019 (38% of total), which was FDA approved in 2017. Similarly, the highest proportional reports for dimethyl fumarate were in 2014 (26.9% of total), shortly after it's FDA approval in 2013. Figure 2 shows the source of alopecia reports for each drug as a proportion of the total reports. Patients initiated reporting for most of the DMTs (78% of total).
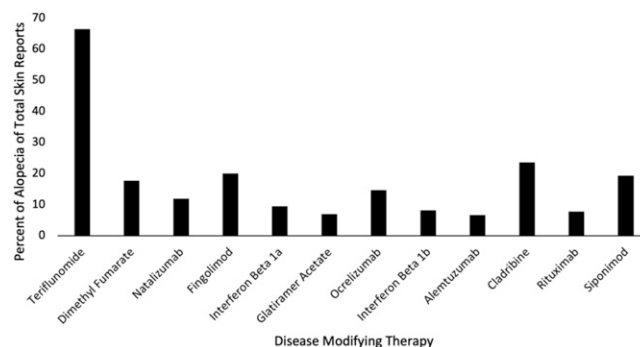
Figure 1. Percent of alopecia out of all reports under skin and subcutaneous tissue disorders for each DMT.

However, in a few DMTs, a comparable proportion of reporting was done by the healthcare professionals and the patient. Those DMTs, included glatiramer acetate (44.7% reported by healthcare professionals), alemtuzumab (53.0% reported by healthcare professionals), rituximab (50% reported by healthcare professionals), and cladribine (50.0% reported by healthcare professionals). Figure 3 shows forest plots of ROR values for total, male, and female alopecia reports. Supplemental Figure 1 shows the age distribution for reports for all the DMTs. A higher proportion of reports at a younger age was observed with alemtuzumab, with most reports in the fourth decade of life.

OpenFDA analyses showed 6508 total reports of alopecia in the drugs studied indicated for MS (Table 2). Significantly increased odds of reporting alopecia and significant IC025

Figure 2. Proportion of report sources concerning alopecia from January 1, 2009 to June 30, 2020 for each multiple sclerosis drug.*Source not specified in 4 reports for teriflunomide, 15 for dimethyl fumarate, 5 for natalizumab, 11 for fingolimod, 10 for interferon beta-1a, 2 for glatiramer acetate, and 2 for interferon beta-1b.

(ROR, 95% confidence interval; IC025) were noted for teriflunomide (18.08, 17.25-18.95; 3.26), alemtuzumab (1.36, 1.12-1.65; .11), and dimethyl fumarate (1.23, 1.16-1.31; .16). When stratifying by sex, increased odds in females and signifi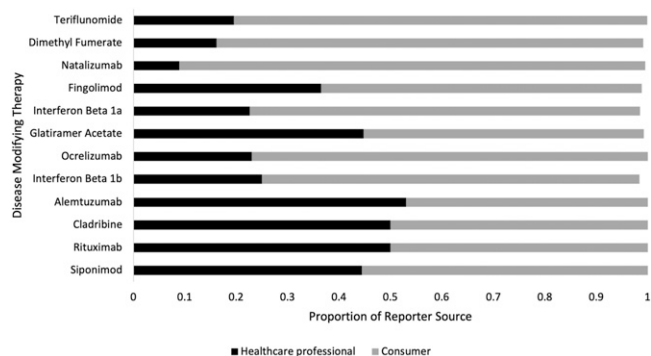cant IC025 were noted for teriflunomide (18.00, 17.12-18.93; 3.22), alemtuzumab (1.43, 1.16-1.76; .15), ocrelizumab (1.28, 1.11-1.49; .1), and dimethyl fumarate (1.26, 1.18-1.34; .18). Increased odds in males with significant IC025 were noted only for teriflunomide (24.65, 20.72-29.31; 3.47).

Discussion

The current study is the first to utilize a large public database to analyze alopecia reports or hair thinning in MS patients treated with various DMTs. While we acknowledge the inherent limitations of the FAERS database, including self-reporting bias, the current report highlights an important and understudied MS therapeutics area. It can be inferred that the reports reflect reasonable validity, supported by a large number of expected alopecia reports in patients treated with teriflunomide, a drug known to be associated with transient alopecia.[9] Teriflunomide associated transient hair loss has been noted in clinical practice and is likely due to premature transition from the anagen to telogen phase, known as telogen effluvium.[16,17] We identified relatively high proportional alopecia reports in most DMTs between 2009 and 2020 compared to overall reports in the skin and subcutaneous disorders category. We further identified trends of more reports in female patients, but no clear association with age, except for the tendency toward younger age in alemtuzumab treated patients. It is possible that these medications cause alopecia more often in females than males. Alternatively, this could reflect a bias in reporting by female patients. Earlier studies suggest that alopecia affects women more adversely in terms of body image and overall psychological well-being compared to males.[18]
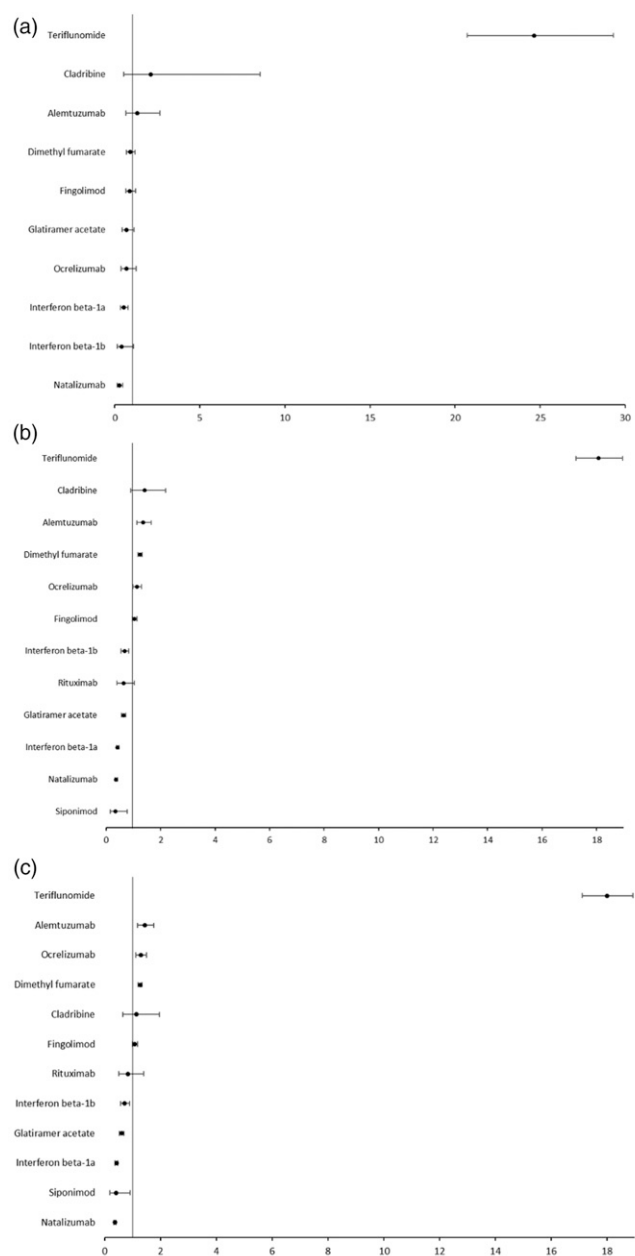
Figure 3. (A) Reporting odds ratios of all alopecia reports, (B) reporting odds ratios of male alopecia reports, (C) reporting odds ratios of female alopecia reports.

Interestingly, reports were sent mostly by patients and families (consumers) for the majority of DMTs. The difference in reporting source may indicate that alopecia is considered an important event by patients and less so by healthcare providers, or possibly patients may become aware of the possible association between DMTs and alopecia through social media and patient groups. Additionally, this could reflect that healthcare providers may have limited awareness that alopecia may be a side effect of various DMTs despite the prescribing label. In the age of social media, it is possible that there is an influence of popular opinion on the database. Any perceived hair loss could be

Table 2. OpenFDA analysis of alopecia reports and sex differences.

DRUG	ALOPECIA EFFECT	DRUG OTHER ADVERSE EVENTS	ALL DRUGS ALOPECIA REPORTS	ALL DRUGS OTHER ADVERSE EVENTS	REPORTING ODDS RATIO (95% CONFIDENCE INTERVAL)	INFORMATION COMPONENT	INFORMATION COMPONENT LOWER LIMIT OF 95% CREDIBLE INTERVAL
Alopecia reports							
Teriflunomide	3091	15 221	5340	475 435	18.08 (17.25-18.95)	3.32	3.26
Dimethyl fumarate	1340	65 120	7091	425 537	1.23 (1.16-1.31)	.26	.16
Fingolimod	718	40 563	7713	450 094	1.03 (.96-1.12)	.04	−.08
Interferon beta-1a	364	47 115	8067	443 542	.42 (.38-.47)	−1.14	−1.31
Glatiramer acetate	277	24 963	8154	465 694	.63 (.56-.71)	−.62	−.82
Natalizumab	277	41 997	8154	448 660	.36 (.32-.41)	−1.36	−1.56
Ocrelizumab	198	10 341	8233	480 316	1.12 (.97-1.29)	.15	−.08
Alemtuzumab	108	4638	8323	486 019	1.36 (1.12-1.65)	.43	.11
Interferon beta-1b	93	8016	8338	482 641	.67 (.55-.82)	−.56	−0.9
Cladribine	20	834	8411	489 823	1.40 (.90-2.18)	.46	−.29
Rituximab	16	1468	8415	489 189	.63 (.39-1.04)	−.63	−1.47
Siponimod	6	1013	8425	489 644	.34 (.15-.77)	−1.45	−2.86
Male alopecia							
Teriflunomide	240	3327	298	101 810	24.65 (20.72-29.31)	3.69	3.47
Dimethyl fumarate	63	13 331	475	91 806	.91 (.70-1.19)	−.11	−.53
Fingolimod	41	8922	497	96 215	.89 (.65-1.22)	−.15	−.67
Interferon beta-1a	25	9087	513	96 050	.52 (.34-.77)	−.88	−1.55
Glatiramer acetate	17	4719	521	100 418	.69 (.43-1.13)	−.49	−1.31
Natalizumab	14	9304	524	95 833	.28 (.16-.47)	−1.73	−2.63
Ocrelizumab	10	2872	528	102 265	.67 (.36-1.26)	−.53	−1.61
Alemtuzumab	8	1193	530	103 944	1.32 (.65-2.65)	.36	−.85
Interferon beta-1b	4	1877	534	103 260	.41 (.15-1.10)	−1.16	−2.93
Cladribine	2	185	536	104 952	2.12 (.52-8.55)	.78	−1.81
Rituximab	0	337	538	104 800	N/A	−2.15	−12.47
Siponimod	0	218	538	104 919	N/A	−1.69	−12.01

(Continued)

Table 2. Continued.

	DRUG ALOPECIA EFFECT	DRUG OTHER ADVERSE EVENTS	ALL DRUGS ALOPECIA REPORTS	ALL DRUGS OTHER ADVERSE EVENTS	REPORTING ODDS RATIO (95% CONFIDENCE INTERVAL)	INFORMATION COMPONENT	INFORMATION COMPONENT LOWER LIMIT OF 95% CREDIBLE INTERVAL
Female alopecia							
Teriflunomide	2754	11 424	4843	361 589	18.00 (17.12-18.93)	3.28	3.22
Dimethyl fumarate	1168	47 102	6429	325 911	1.26 (1.18-1.34)	.28	.18
Fingolimod	666	30 607	6931	342 406	1.07 (.99-1.16)	.09	−.03
Interferon beta-1a	330	36 723	7267	336 290	.42 (.37-.46)	−1.16	−1.34
Natalizumab	246	31 634	7351	341 379	.36 (.32-.41)	−1.37	−1.58
Glatiramer acetate	242	19 320	7355	353 693	.60 (.53-.69)	−.69	−0.9
Ocrelizumab	182	6994	7415	366 019	1.28 (1.11-1.49)	.34	0.1
Alemtuzumab	93	3200	7504	369 813	1.43 (1.16-1.76)	0.5	.15
Interferon beta-1b	87	6011	7510	367 002	.71 (.57-.88)	−.48	−.84
Rituximab	15	882	7582	372 131	.83 (.50-1.39)	−.25	−1.12
Cladribine	13	564	7584	372 449	1.13 (.65-1.96)	.17	−.77
Siponimod	6	719	7591	372 294	.41 (.18-.91)	−1.2	−2.62

misattributed to popular DMTs in the social space since there is no method to verify these reports.

Interferon Beta-1a & Interferon Beta-1b

There were 659 reports of alopecia associated with interferon beta-1a and 124 reports with interferon beta-1b.[18] Mild alopecia was reported in 4% of patients as a possible side effect within prescription instructions for interferon beta-1a[10] and interferon beta-1b.[10,11,19] Associations of telogen effluvium with increased pro-inflammatory cytokines and the presence of autoimmune diseases have been previously reported, indicating possible immunological involvement.[20] The mechanism of interferon-beta action is complex; however, current literature describes the downregulation of T cell activation and pro-inflammatory cytokines.[21] This is counterintuitive to immunological explanations for telogen effluvium. Additionally, the reporting odds ratios in our study did not show an increased odd of reporting alopecia with the interferons, contrary to what would be expected. The most plausible explanation is that reporting to FAERS decreases for specific drugs over time, weakening the statistical analyses for older drugs like the interferons. Another explanation that would be more congruent to the immunological explanations of telogen effluvium is that interferons may actually decrease risk of alopecia. Additionally, recent knockout studies in ACKR2$^{-/-}$ mice revealed the importance of interferon-beta in the rescue of collagen organization and hair loss.[22] However, due to alopecia reports in the literature and prescription label for the interferons, further exploration is warranted.

Dimethyl Fumarate

A single case study of a 55-year-old woman experiencing transient hair loss associated with dimethyl fumarate treatment was published in 2016.[23] Our findings indicate a surprisingly large number of alopecia reports for this drug (a total of 1675), rendering dimethyl fumarate as the second most reported DMT in association with alopecia. Additionally, odds ratio analyses show an increased odd of alopecia in females, but not males. Dimethyl fumarate is a well-known activator of the Nrf2 antioxidant pathway.[24] Prolonged genetic and pharmacological activation of Nrf2 in mouse keratinocytes has been previously shown to cause hair loss.[25] However, in situ studies of human scalp hair follicles support that the activation of Nrf2 protects against oxidative stress-induced hair growth inhibition.[26] Nrf2 involvement, if any, is purely speculative and further studies are required to assess for biological explanations for dimethyl fumarate and alopecia. In a non-placebo-controlled pilot study, 6 out of 10 patients experienced significant improvement of their alopecia areata with a 6-month dimethyl fumarate treatment.[27] This is counterintuitive to the number of reports of alopecia we present in this study. Further investigations into the systematic effects of dimethyl fumarate are necessary to explain the conflicting literature.

Fingolimod

Fingolimod had 926 reports of alopecia over the 10-year study from 2009 to June, 2020. In fingolimod pivotal trials, alopecia was reported in 3 patients and 2 patients on placebo as a side effect.[28-30] Previous studies in mice show that S1P2 receptor signaling is required to maintain hair cells.[31] Fingolimod binds non-specifically to the S1P receptor, with preference to subtypes 1, 3, and 5.[32] Therefore, it may not have a role in hair cell maintenance due to S1P subtype affinity, supported by the lack of significance in our odds ratio analysis.

Siponimod

Siponimod is similar to fingolimod in its mechanism of action by targeting the S1P receptor, however it is more selective for S1P1 and S1P5 receptors.[33] The phase III clinical trials for siponimod did not show an association with alopecia.[34] Additionally, current literature review does not show any reports of alopecia with siponimod. We found 36 reports of alopecia; however, there were no increased odds during statistical analysis. Further data collection and post-market surveillance is required to confirm the lack of relationship between siponimod and alopecia.

Alemtuzumab

All MS drugs studied showed a normal distribution for age except for alemtuzumab, which displayed a disproportionally high number of reports in the fourth decade of life. It might be possible that this drug is associated with a greater frequency of alopecia in younger individuals, but the mechanism is unclear.

To date, there have been 5 case studies describing alopecia with alemtuzumab use. Recurrent and universal alopecia areata was reported following alemtuzumab treatment in a 28-year-old female and 27-year-old male patient.[35] An additional case of alopecia areata has been reported in a 31-year-old patient with relapsing-remitting MS.[36] Alopecia universalis has been reported in 3 cases of patients treated with alemtuzumab for MS.[37,38] Patchy alopecia was reported in a 34-year-old woman being treated for MS.[39] However, it is important to note that this patient was on thiamazole treatment for thyroid disease. Lastly, 1 case of recurrent alopecia totalis was described in a large, high disability, treatment-refractory MS clinic cohort.[40] Our odds ratio analysis showed increased odds of alopecia with alemtuzumab in females (1.43), but not males; however, it is important to note that reports from males were scarce (8). A possible contributing factor for alopecia and alemtuzumab is possible autoimmune thyroid disease following alemtuzumab therapy, since thyroid dysfunction is known to contribute to alopecia.[41,42] Our findings add to the current literature on a possible association of alopecia with alemtuzumab therapy and raise a question of whether secondary autoimmunity may be behind the observed alopecia following alemtuzumab treatment.

Natalizumab

To our knowledge, 1 case study reported alopecia barbae in a 39-year-old male presenting with alopecia barbae after long-term natalizumab therapy, which improved after drug discontinuation.[43] Here, we found 985 additional reports, although no increased odds were noted. Studies in mice demonstrated an essential role of integrins, specifically β1, in hair follicles' growth and maintenance.[44] Natalizumab is a humanized monoclonal antibody that works by binding to α4β1-integrin.[45] While integrins have an essential role in hair follicle maintenance, the interactions between natalizumab and the specific integrins responsible for preventing alopecia are unknown and require investigation.

Ocrelizumab

Previously, 6 reports of alopecia areata following ocrelizumab therapy have been reported.[46,47] We found 243 reports, mostly in 2019, suggesting a possible association. Additionally, there were increased odds in female patients. Interestingly, administration of other anti-CD20 antibodies has been previously associated with hair loss.[48] Since ocrelizumab is a second-generation anti-CD20 antibody,[49] we can infer that it is possible for ocrelizumab to be associated with further alopecia reports. However, further studies are needed with ocrelizumab, specifically to explore these exact mechanisms and associations.

Glatiramer Acetate

We found 257 reports of alopecia with glatiramer acetate use; however, there were no increased odds in males or females. A previous case study reported a 42-year-old woman with relapsing-remitting MS who developed alopecia with glatiramer acetate.[50] Previous in vitro studies show that glatiramer acetate can bind to HLA-DR, an MHC class II cell surface receptor.[51] Alopecia has known associations with aberrant HLA-DR expression in hair follicles.[52] Additionally, a transmission disequilibrium test revealed an association between alopecia areata and class II MHC loci, including HLA-DR.[53] However, no conclusive biological explanations of glatiramer acetate and alopecia can be made without further investigation.

Cladribine

A recently approved therapy for MS, cladribine, is known to be associated with alopecia. In the pivotal clinical trial, 3.3% of patients treated with cladribine reported hair loss, compared to 1.1% of those who received placebo.[54,55] Here we show 24 reports of alopecia with cladribine, however there were no increased odds. It is important to note that the low sample size may not allow for sufficient statistical power.

Alopecia and MS

Earlier studies do not support an association of alopecia with MS. However, a study of 70 patients with MS reported on 5 cases of associated alopecia areata that developed after the onset of MS.[56] It is important to note that in addition to MS, all patients with alopecia areata had other comorbid autoimmune diseases such as Hashimoto's thyroiditis, uveitis, bronchial asthma, and hives. Another case study reported a Caucasian female affected by alopecia Universalis, autoimmune thyroiditis, MS, and pelvic endometriosis.[57] Alopecia Universalis occurred at age 13 and the onset of MS at age 27. Lastly, alopecia areata were reported in 2 females affected by MS, aged 45 and 32.[58] Onset of alopecia occurred many years before the onset of MS in these patients. Although the descriptive analysis of alopecia in this study may be related to features of MS, current evidence does not indicate a link between MS and alopecia.

Both alopecia and MS exhibit genetic predisposition, environmental triggers, and similar pathological processes.[58] Our study further reinforces the importance of considering alopecia in patients affected by MS, with particular care when deciding which DMT to utilize or follow up with patients if any concerns regarding hair loss develop throughout treatment.

Study Limitations

The current study has limitations due to its retrospective design. Additionally, the FAERS and OpenFDA database possess inherent reporting bias. Adverse events are voluntarily reported by health care professionals and consumers, therefore leading to possible overreporting, underreporting, and duplication of reporting. It is important to note that androgenic alopecia is common, and the risk increases with age in the general population.[7] Due to the self-reported nature of this data, there is a possible attribution bias. However, statistical analyses using OpenFDA provides comparison across all drugs which could control for this bias, in theory. This data is based on spontaneous reports and can only indicate the possibility of adverse events; no conclusions can be made about the incidence rates or causality. Also, no association can be made with the duration of being on the therapy. Reports have not been filtered to account for polytherapy or reported suspected drug associated with alopecia. Alopecia reports in the database are predominantly classified as the general keyword "alopecia". Therefore, it is not possible to determine disproportionality of different forms of alopecia. However, the FAERS and OpenFDA database are valuable tools to examine trends, proportions, and patterns during post-market surveillance.

Conclusions

Aside from teriflunomide, interferon beta-1a, and interferon beta-1b, there is a lack of knowledge about alopecia or hair thinning as a potential side effect of currently used MS DMTs. We provided the first detailed report on the subject based on a publicly available database. The vast majority of reports were

submitted by patients. The FAERS database provides a mechanism for patients to share their experiences regarding pharmacological treatments. Statistical analyses showed increased odds of reporting alopecia with teriflunomide in both males and females, and increased odds of reporting alopecia for alemtuzumab, dimethyl fumarate, and ocrelizumab in females only. Our findings of alopecia reports across all DMTs examined calls for further investigation into the subject, especially regarding sex differences. We further advise discussing hair thinning or alopecia as a possible side effect observed with all DMTs and encourage reporting to the FAERS.

Authors' Contributions

MHP: Major role in data acquisition, data analysis and interpretation and drafting the initial manuscript.AS: Data analysis, interpretation and critical review of manuscript.DP: Data collection, data analysis and critical review of manuscript.AZO: Study concept, data analysis, data interpretation. critical review of the manuscript, and approval of final version for submission.

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REFERENCES

1. Nylander A, Hafler DA. Multiple sclerosis. *J Clin Invest*. 2012;122(4):1180-1188. doi:10.1172/JCI58649
2. Cree BAC, Mares J, Hartung HP. Current therapeutic landscape in multiple sclerosis: An evolving treatment paradigm. *Curr Opin Neurol*. 2019;32(3):365-377.
3. Hunt N, McHale S. The psychological impact of alopecia. *Br Med J*. 2005; 331(7522):951-953. doi:10.1136/BMJ.331.7522.951
4. Lin J, Saknite I, Valdebran M, et al. Feature characterization of scarring and non-scarring types of alopecia by multiphoton microscopy. *Laser Surg Med*. 2019;51(1): 95-103. doi:10.1002/LSM.23017
5. Shapiro J. Clinical practice. Hair loss in women. *N Engl J Med*. 2007;357(16): 1620-1630. doi:10.1056/NEJMCP072110
6. Piraccini BM, Alessandrini A. Androgenetic alopecia. *G Ital Dermatol Venereol*. 2014;149(1):15-24. doi:10.5005/jp/books/14121_10
7. Esen Salman K, Kucukunal NA, Kivanc Altunay I, Cerman AA, Aksu Cerman A. Frequency, severity and related factors of androgenetic alopecia in dermatology outpatient clinic: Hospital-based cross-sectional study in Turkey. *An Bras Dermatol*. 2017;92(1):35-40. doi:10.1590/ABD1806-4841.20175241
8. Lee HH, Gwillim E, Patel KR, et al. Epidemiology of alopecia areata, ophiasis, totalis, and universalis: A systematic review and meta-analysis. *J Am Acad Dermatol*. 2020;82(3):675-682. doi:10.1016/J.JAAD.2019.08.032
9. Chan A, De Seze J, Comabella M. Teriflunomide in patients with relapsing-remitting forms of multiple sclerosis. *CNS Drugs*. 2016;30(1):41-51. doi:10.1007/S40263-015-0299-Y
10. Avonex. *Avonex (Interferon Beta-1a), Prescribing Information*. Cambridge, MA: Biogen Inc.; 1996.
11. Betaseron. *Betaseron (Interferon Beta-1b), Prescribing Information*. Richmond, CA: Berlex Laboratories; 1993.
12. Food US, Administration Department. *Questions and Answers on FDA's Adverse Event Reporting System (FAERS)*. Silver Spring, MD: Food and Drug Administration. https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm Updated June. 4.
13. Bate A, Evans SJW. Quantitative signal detection using spontaneous ADR reporting. *Pharmacoepidemiol Drug Saf*. 2009;18(6):427-436. doi:10.1002/PDS.1742
14. Bomze D, Hasan Ali O, Bate A, Flatz L. Association between immune-related adverse events during anti–PD-1 therapy and tumor mutational burden. *JAMA Oncol*. 2019;5(11):1633-1635. doi:10.1001/JAMAONCOL.2019.3221
15. Park J, Jung H, Heo SJ, Jung I. Comparison of data mining methods for the signal detection of adverse drug events with a hierarchical structure in postmarketing surveillance. *Life*. 2020;10(8):1-22. doi:10.3390/LIFE10080138
16. Hendin Travis L, Okai A, Cavalier S, Stam D, Farnett L, Edwards KR. Real-world observational evaluation of hair thinning in patients with multiple sclerosis receiving teriflunomide: Is it an issue in clinical practice? *Neurol Ther*. 2018;7(2):341-347. doi:10.1007/S40120-018-0107-Y
17. O'Connor P, Comi G, Freedman MS, et al. Long-term safety and efficacy of teriflunomide. *Neurology*. 2016;86(10):920-930. doi:10.1212/WNL.0000000000002441
18. Cash TF, Price VH, Savin RC. Psychological effects of androgenetic alopecia on women: Comparisons with balding men and with female control subjects. *J Am Acad Dermatol*. 1993;29(4):568-575. doi:10.1016/0190-9622(93)70223-G
19. Walther EU, Hohlfeld R. Multiple sclerosis: Side effects of interferon beta therapy and their management. *Neurology*. 1999;53(8):1622-1627. doi:10.1212/WNL.53.8.1622
20. Rebora A. Telogen effluvium: A comprehensive review. *Clin Cosmet Invest Dermatol*. 2019;12:583-590.
21. Chofflon M. Mechanisms of action for treatments in multiple sclerosis: Does a heterogeneous disease demand a multi-targeted therapeutic approach? *BioDrugs*. 2005;19(5):299-308.
22. Butenko S, Ben Jashar N, Sheffer T, Sabo E, Schif-Zuck S, Ariel A. ACKR2 limits skin fibrosis and hair loss through IFN-β. *Faseb J*. 2021;35(10):e21917. doi:10.1096/FJ.202002395RR
23. Losavio FA, Lucchini M, De Fino C, Mirabella M, Nociti V. Transient hair loss during treatment with dimethyl-fumarate for multiple sclerosis. *Mult Scler Relat Disord*. 2016;7:68-69.
24. Linker RA, Lee DH, Ryan S, et al. Fumaric acid esters exert neuroprotective effects in neuroinflammation via activation of the Nrf2 antioxidant pathway. *Brain*. 2011; 134(Pt 3):678-692.
25. Schäfer M, Willrodt AH, Kurinna S, et al. Activation of Nrf2 in keratinocytes causes chloracne (MADISH)-like skin disease in mice. *EMBO Molec Med*. 2014;6(4): 442-457. doi:10.1002/emmm.201303281
26. Haslam IS, Jadkauskaite L, Szabó IL, et al. Oxidative damage control in a human (Mini-) organ: Nrf2 activation protects against oxidative stress-induced hair growth inhibition. *J Invest Dermatol*. 2017;137(2):295-304. doi:10.1016/j.jid.2016.08.035
27. Venten I, Hess N, Hirschmüller A, Altmeyer P, Brockmeyer N. Treatment of therapy-resistant alopecia areata with fumaric acid esters. *Eur J Med Res*. 2006;11(7): 300-305.
28. Kappos L, Radue EW, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med*. 2010;362(5):387-401.
29. Calabresi PA, Radue EW, Goodin D, et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): A double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Neurol*. 2014;3(6): 545-556. doi:10.1016/S1474-4422(14)70049-3
30. Khatri BO. Fingolimod in the treatment of relapsing-remitting multiple sclerosis: Long-term experience and an update on the clinical evidence. *Ther Adv Neurol Disord*. 2016;9(2):130-147. doi:10.1177/1756285616628766
31. Herr DR, Grillet N, Schwander M, Rivera R, Müller U, Chun J. Sphingosine 1-phosphate (S1P) signaling is required for maintenance of hair cells mainly via activation of S1P2. *J Neurosci*. 2007;27(6):1474-1478. doi:10.1523/JNEUROSCI.4245-06.2007
32. Chun J, Hartung HP. Mechanism of action of oral fingolimod (FTY720) in multiple sclerosis. *Clin Neuropharmacol*. 2010;33(2):91-101. doi:10.1097/WNF.0b013e3181cbf825
33. Pan S, Gray NS, Gao W, et al. Discovery of BAF312 (Siponimod), a potent and selective S1P receptor modulator. *ACS Med Chem Lett*. 2013;4(3):333-337. doi:10.1021/ML300396R
34. Kappos L, Bar-Or A, Cree BAC, et al. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): A double-blind, randomised, phase 3 study. *Lancet*. 2018;391(10127):1263-1273. doi:10.1016/S0140-6736(18)30475-6
35. Alcalá C, Pzére-Miralles F, Gasc F, et al. Recurrent and universal alopecia areata following alemtuzumab treatment in multiple sclerosis: A secondary autoimmune disease. *Mult Scler Relat Disord*. 2019;27:406-408. doi:10.1016/J.MSARD.2018.12.005
36. Dikeoulia E, Neufeld M, Pawlitzki M, Böhm M. Alemtuzumab-induced alopecia areata – a case report and systematic literature review of adverse events associated with Alemtuzumab. *J Dtschn Dermatol Ges*. 2021;19(8):1159-1163. doi:10.1111/DDG.14448
37. Zimmermann J, Buhl T, Müller M. Alopecia universalis following alemtuzumab treatment in multiple sclerosis: A barely recognized manifestation of secondary autoimmunity-report of a case and review of the literature. *Front Neurol*. 2017;8:569.

38. Borriello G, Ianniello A, Toosy AT. Alopecia universalis occurring after alemtuzumab treatment for multiple sclerosis. A two-year follow-up of two patients. *Int J Environ Res Publ Health*. 2021;18(14):7338. doi:10.3390/IJERPH18147338

39. Tsourdi E, Gruber M, Rauner M, Blankenburg J, Ziemssen T, Hofbauer LC. Graves' disease after treatment with alemtuzumab for multiple sclerosis. *Hormones*. 2015;14(1):148-153.

40. Ghodasara RS, Smith SRS, Mosley M, et al. Serious adverse events (SAE), autoimmunity (AI), and infections following alemtuzumab (ALE) therapy in a large, high disability, treatment-refractory MS clinic cohort. *ECTRIMS Online Library*. 2016. 145865; 1182.

41. Daniels GH, Vladic A, Brinar V, et al. Alemtuzumab-related thyroid dysfunction in a phase 2 trial of patients with relapsing-remitting multiple sclerosis. *J Clin Endocrinol Metab*. 2014;99(1):80-89. doi:10.1210/JC.2013-2201

42. Han TY, Lee JH, Noh TK, et al. Alopecia areata and overt thyroid diseases: A nationwide population-based study. *J Dermatol*. 2018;45(12):1411-1417. doi:10.1111/1346-8138.14648

43. Nelson JR, Kazimirchik A, McGowan S, Vorobeychik G. Alopecia Barbae after longterm natalizumab therapy. In: Poster Presented at: Consortium of Multiple Sclerosis Centers Annual Meeting.

44. Bouvard D, Brakebusch C, Gustafsson E, et al. Functional consequences of integrin gene mutations in mice. *Circ Res*. 2001;89(3):211-223. doi:10.1161/hh1501.094874

45. Hutchinson M. Natalizumab: A new treatment for relapsing remitting multiple sclerosis. *Ther Clin Risk Manag*. 2007;3(2):259-268.

46. Chin LD, AbuHilal M. Ocrelizumab-induced alopecia areata-A series of five patients from Ontario, Canada: A case report. *SAGE Open Med Case Rep*. 2020;8:2050313X2091961. doi:10.1177/2050313X20919614

47. Fernandez-Diaz E, Perez-Vicente JA, Villaverde-Gonzalez R, et al. Real-world experience of ocrelizumab in multiple sclerosis in a Spanish population. *Ann Clin Transl Neurol*. 2021;8(2):385-394. doi:10.1002/ACN3.51282

48. Johnston HF, Xu Y, Racine JJ, et al. Administration of anti-CD20 mAb is highly effective in preventing but ineffective in treating chronic graft-versus-host disease while preserving strong graft-versus-leukemia effects. *Biol Blood Marrow Transplant*. 2014;20(8):1089-1103. doi:10.1016/j.bbmt.2014.04.028

49. Sorensen PS, Blinkenberg M. The potential role for ocrelizumab in the treatment of multiple sclerosis: Current evidence and future prospects. *Ther Adv Neurol Disord*. 2016;9(1):44-52.

50. Pacheco MF, Jacobe H, Eagar TN, Stüve O. Reversible alopecia associated with glatiramer acetate. *Arch Neurol*. 2010;67(9):1154.

51. Fridkis-Hareli M, Strominger JL. Promiscuous binding of synthetic copolymer 1 to purified HLA-DR molecules. *Mult Scler J*. 2016;3(6):405. doi:10.1177/135245859700300616

52. Messenger AG, Bleehen SS. Expression of HLA-DR by anagen hair follicles in alopecia areata. *J Invest Dermatol*. 1985;85(6):569-572. doi:10.1111/1523-1747.ep12277414

53. de Andrade M, Jackow CM, Dahm N, Hordinsky M, Reveille JD, Duvic M. Alopecia areata in families: Association with the HLA locus. *J Invest Dermatol Symp Proc*. 1999;4(3):220-223.

54. Giovannoni G, Comi G, Cook S, et al. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. *N Engl J Med*. 2010;362(5):416-426.

55. Cook S, Vermersch P, Comi G, et al. Safety and tolerability of cladribine tablets in multiple sclerosis: The CLARITY (CLAdRIbine Tablets treating multiple sclerosis orallY) study. *Mult Scler*. 2011;17(5):578-593. doi:10.1177/1352458510391344

56. Tada Y, Hamaguchi T, Ikeda Y, Kazuya T, Yamada M. Multiple sclerosis and alopecia areata. *J Neurol Sci*. 2017;381:1064. doi:10.1016/J.JNS.2017.08.3007

57. Alviggi C, Carrieri PB, Pivonello R, et al. Association of pelvic endometriosis with alopecia universalis, autoimmune thyroiditis and multiple sclerosis. *J Endocrinol Invest*. 2006;29(2):182-189.

58. Rossi A, Muscianese M, Federico A, et al. Associations between alopecia areata and multiple sclerosis: A report of two cases and review of the literature. *Int J Dermatol*. 2020;59(4):490-493.