

Utilization and Treatment Patterns of Disease-Modifying Therapy in Pediatric Patients with Multiple Sclerosis in the United States

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Background: The current landscape and treatment patterns of disease-modifying therapy (DMT) use in pediatric patients with multiple sclerosis (MS) are not yet well understood. This study examined DMT utilization and treatment patterns in pediatric patients newly diagnosed as having MS.

Methods: Pediatric patients (<18 years old) with two MS diagnosis claims from January 1, 2010, to December 31, 2016, were identified from the MarketScan Commercial Database. The index date was defined as the date of first MS diagnosis, and patients were followed up for 1 year post-index date. Outcomes evaluated included percentage of patients who initiated treatment after MS diagnosis, different DMTs initiated, treatment discontinuation, and switching treatment during follow-up.

Results: Of 182,057 patients newly diagnosed as having MS, 288 pediatric patients (mean age, 14 years; 61% female) were identified. Within the first year of diagnosis, 188 patients (65.3%) did not receive any DMT. The most common first-initiated treatments were interferons and glatiramer acetate (83%), but 28% of patients switched or discontinued from first-initiated treatment within 6 months of treatment initiation.

Conclusions: This study suggests that a considerable proportion of pediatric patients with MS remain untreated within 1 year of diagnosis. Patients most commonly initiated injectables as their first DMT. Overall, therapy failed early in approximately one in three patients. Thus, the study warrants urgency in treating these patients with currently approved treatment options. *Int J MS Care.* 2021;23:101-105.

The onset of pediatric multiple sclerosis (MS) is reported in approximately 3% to 10% of all patients with MS in the United States.¹ Most pediatric patients with MS (85%) have a relapsing-remitting disease course, have a high relapse rate,^{2,3} and reach disability at a younger age compared with the

adult MS population. Multiple sclerosis also affects cognitive abilities, with approximately 50% of children and adolescents older than 11 years reporting the need to repeat a grade in school after their first MS attack.⁴

Consensus statements providing recommendations for pharmacologic treatments in children and adolescents with MS are based on limited supporting evidence from the observational studies on the effectiveness of disease-modifying therapies (DMTs) in this population.^{5,6} Currently, more than a dozen treatments approved by the US Food and Drug Administration are available for adult patients with MS. However, fingolimod is currently the first and only DMT approved (in March 2018) for the treatment of pediatric patients with MS in the United States. In ongoing randomized trials in the pediatric population, the safety and efficacy of teriflunomide is being assessed against placebo (clinicaltrials.gov

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identifier: NCT02201108), and that of dimethyl fumarate is being evaluated against interferon beta-1a (NCT02283853).⁷ It has been observed that early initiation of treatment in adult patients with MS is associated with better outcomes.⁸ Moreover, in patients in whom platform injectable agents (glatiramer acetate, interferon beta-1a, and interferon beta-1b) might be less tolerable and might not be able to control the disease adequately, escalation to newer DMTs (Table 1) can be considered.⁹

The role of newer DMTs in the management of pediatric MS is yet to be well defined. In addition, the current landscape and treatment patterns of DMT use in pediatric patients are not yet well understood, which leads clinicians to face considerable uncertainty regarding the best treatment plan for these patients. Therefore, it is important to understand the current distribution of DMT utilization and treatment patterns in pediatric patients with MS.

Methods

Study Design

A retrospective observational study was conducted using administrative claims data from the US Truven Health Analytics MarketScan Commercial and Encounters Database from July 1, 2009, to December 31, 2017. The database includes health care plan enrollment history and medical (inpatient and outpatient) and pharmacy claims data for insured employees and their dependents from more than 130 employers that sponsor private insurance, representing approximately 40 million lives covered annually across all geographic regions. Because data collection was retrospective from insurance claims and was deidentified, there was no institutional review board approval, ethics review, or consent required for the study.

Pediatric patients (aged <18 years) with at least two MS diagnosis claims (per *International Classification of Diseases [ICD], Ninth Revision* code 340.XX; *ICD-10* code G35) during the identification period from January 1, 2010, to December 31, 2016, were included in the study. The date of the first MS diagnosis was defined as the index date (Figure S1, which is published in the online version of this article at ijmsc.org). Patients were required to have medical and pharmacy benefits during the 6 months pre-index date and 1 year post-index date. In addition, patients with DMT use prior to 6 months before the first MS diagnosis (index date) were excluded.

Table 1. Classification of disease-modifying therapies

Treatment classification	Disease-modifying therapy
Platform injectables	Glatiramer acetate; interferon beta-1a and interferon beta-1b
Newer agents, oral	Dimethyl fumarate, fingolimod, teriflunomide
Other newer agents	Alemtuzumab, daclizumab (drug withdrawn from market), natalizumab, ocrelizumab

Study Outcomes

Patient characteristics captured in the baseline (pre-index) period included age on index date, sex, region (Midwest, Northeast, South, West), insurance type (fee-for-service, health maintenance organization, point-of-service capitation), and pre-index comorbidity using the Charlson Comorbidity Index.¹⁰ The main outcomes were frequencies and proportions of treated and untreated pediatric patients with MS (untreated was defined as no DMT use in the 1 year after the first MS diagnosis). Secondarily, the distribution of first-initiated DMT after MS diagnosis was evaluated. Switching was examined for first-initiated DMTs and was defined as the start of a new DMT within 60 days of the end of the first-initiated DMT during 1-year follow-up. In addition, time to switch was defined as the number of months between the first fill and the fill for the subsequent DMT within 60 days. Discontinuation of treatment was measured as a therapy gap of at least 60 days after first-initiated DMT during follow-up.

Statistical Analyses

All analyses were performed using SAS version 9.3 (SAS Institute Inc). Patients' baseline characteristics were summarized overall and according to patients treated and untreated with DMTs. All categorical variables are reported as frequencies and percentages. Continuous variables are reported as mean \pm SD, median (interquartile range), and range.

Results

Of the 182,057 newly diagnosed patients with MS during the study identification period, 817 were younger than 18 years. Among these, 438 patients were continuously enrolled with medical and pharmacy benefits during the 6-month pre-index period and 326 patients had 1-year post-index date follow-up data. After applying the final inclusion criteria (no DMT use in the pre-index baseline period), 288 newly diagnosed pediatric patients with MS were included in the study cohort (Figure S2).

DMT Utilization

Of the 288 patients who were included in the final cohort of newly diagnosed patients with MS, 188 (65.3%) remained untreated 1 year after their MS diagnosis. The remaining 100 (34.7%) were treated with DMTs during follow-up.

Baseline Characteristics

In the overall cohort (N = 288), the mean \pm SD age of patients was 13.9 \pm 3.6 years, and 175 (60.8%) of them were female (Table 2). Geographically, the population was representative across the US regions (Midwest, Northeast, South, and West). The mean \pm SD Charlson Comorbidity Index score for the cohort was 0.3 \pm 0.7. The proportion of females was higher in the treated group versus the untreated group (75.0% vs 53.2%). A comparatively higher proportion of DMT-treated patients had insurance coverage by health maintenance organization and point-of-service capitation insurance (24.0% [n = 24] vs 10.1% [n = 19]).

Table 2. Baseline characteristics of included pediatric patients

Characteristic	Overall (N = 288)	Treated with DMTs (n = 100)	Untreated with DMTs (n = 188)
Age, y			
Mean \pm SD	13.9 \pm 3.6	15.0 \pm 2.5	13.3 \pm 4.0
Median [IQR]	15.0 [5.0]	16.0 [3.0]	15.0 [5.0]
Range	2.0-17.0	4.0-17.0	2.0-17.0
Sex			
Male	113 (39.2)	25 (25.0)	88 (46.8)
Female	175 (60.8)	75 (75.0)	100 (53.2)
US Region			
Northeast	53 (18.4)	14 (14.0)	39 (20.7)
Midwest	72 (25.0)	27 (17.0)	45 (23.9)
South	119 (41.3)	42 (42.0)	77 (41.0)
West	42 (14.6)	17 (17.0)	25 (13.3)
Unknown	2 (0.7)	0	2 (1.1)
Insurance type			
Fee-for-service	242 (84.0)	76 (76.0)	166 (88.3)
HMO and POS capitation	43 (14.9)	24 (24.0)	19 (10.1)
Unknown	3 (1.0)	0	3 (1.6)
Charlson Comorbidity Index ^a			
Mean \pm SD	0.3 \pm 0.7	0.2 \pm 0.6	0.3 \pm 0.8
Range	0.0-7.0	0.0-2.0	0.0-7.0

Note: Unless otherwise indicated, values are given as number (percentage).

Abbreviations: DMT, disease-modifying therapy; HMO, health maintenance organization; IQR, interquartile range; POS, point-of-service.

^aMedian [IQR] Charlson Comorbidity Index values were 0.0 [0.0] for the three table columns.

First-Initiated Treatment

During 1-year follow-up, 100 patients initiated their first DMT after diagnosis of MS. Two of these patients were excluded due to inadequate data. Of the 98 patients receiving the first-initiated treatment included in the analysis, 81 (82.7%) received platform injectables, such as glatiramer acetate (n = 47 [48.0%]), interferon beta-1a (n = 30 [30.6%]), and interferon beta-1b (n = 4 [4.1%]). Other first-initiated treatments received were newer oral agents, such as dimethyl fumarate (n = 7 [7.1%]), fingolimod (n = 4 [4.1%]), and other remaining agents such as natalizumab (n = 5 [5.1%]) and peginterferon beta-1a (n = 1 [1.0%]) (Table 3).

Switching and Discontinuation

Of the 98 patients who initiated their first DMT, 19 (19.4%) switched to a second-line DMT within the 1-year follow-up period. The median time to switch to another therapy was 5.8 months.

Of the remaining 76 patients (with a few outlier patients excluded), nine discontinued treatment. The

Table 3. Switching and discontinuation rates in pediatric patients studied

Outcome	Data
First-initiated DMT agent utilization (N = 98)	
Glatiramer acetate	47 (48.0)
Interferon beta-1a	30 (30.6)
Dimethyl fumarate	7 (7.1)
Natalizumab	5 (5.1)
Interferon beta-1b	4 (4.1)
Fingolimod	4 (4.1)
Peginterferon beta-1a	1 (1.0)
Switching (n = 98)	
Proportion of patients who switched	19 (19.4)
Time to switch, mo (n = 19)	
Mean \pm SD	6.2 \pm 2.6
Median [IQR], range	5.8 [4.5], 2.3-11.5
Discontinuation (n = 76)	
Proportion of patients who discontinued	9 (11.8)
Time to discontinuation, mo (n = 9)	
Mean \pm SD	4.4 \pm 2.4
Median [IQR], range	3.8 [2.6], 0.2-9.4

Note: Values are given as number (percentage) unless otherwise indicated.

Abbreviations: DMT, disease-modifying therapy; IQR, interquartile range.

median time to discontinue among these patients was 3.8 months (Table 3). Overall, approximately 28% of patients either discontinued or switched from their first-initiated DMT during the first 6 months (Table S1).

Discussion

This real-world retrospective study presents findings on current DMT utilization by treatment status, first-initiated DMT after MS diagnosis, switching to other DMTs, and treatment discontinuation in pediatric patients within 1 year of MS diagnosis in an insured US managed care population. We found that approximately 65% of pediatric patients with MS were not treated within the first year of MS diagnosis. Although patients who were treated after diagnosis were most commonly prescribed interferons and glatiramer acetate, a few patients had treatment failure (switched or discontinued) early after initiation of their first DMT for MS.

This study showed that a considerable proportion of pediatric patients with MS remained untreated within the first year of MS diagnosis in a nationally representative population. The existing literature shows that the proportion of pediatric patients with MS not receiving any treatment varies from 17% to 90% across multiple observational studies conducted in the United States.¹¹⁻¹⁵ These varying estimates might be due to the heterogeneity of the data sources analyzed and the follow-up duration considered. Moreover, the existing data are based

on studies conducted at specific regional centers with small sample sizes, leading to limited generalizability and geographic distribution.

In the literature, information on reasons for not undergoing treatment after MS diagnosis is limited in the pediatric population. The low treatment rate may be attributed to the limited information available to the clinicians due to the scarcity of clinical trials in the pediatric setting.¹⁶ Moreover, in adults, a study based on a regional health plan assessed the perceptions of patients with MS not currently treated with DMTs by using the Multiple Sclerosis Medication Questionnaire. In that study, it was observed that adverse effects and potential high costs were barriers to DMT use, as agreed by most of the patients. Decisions regarding treatment versus no treatment largely tend to depend on the physician's perception of the DMTs.¹⁶ In another observational study that assessed the impact of early treatment with DMTs (interferon beta-1b) in adult patients with MS who were enrolled in a pivotal trial conducted in North America and followed up for 21.4 years in a real-world setting, a significant survival advantage was observed in the DMT group compared with the placebo group, suggesting a need for DMT initiation.¹⁷ These studies might provide some insights on treatment behavior, although we acknowledge that additional studies need to be conducted specifically in pediatric treatments.

The most common first-initiated DMTs in the present study were platform injectables, and newer DMTs were used in 17.3% of patients. Approximately 19% of patients switched from their first-initiated DMT within 6 months. A recently published study by Young and colleagues¹¹ of male pediatric patients with relapsing-remitting MS at the University of California San Francisco Regional Pediatric MS Center found that 71% of the treated patients received platform injectables during 3.17 years of follow-up. A retrospective study conducted at pediatric centers of excellence in the United States observed that more than 95% of patients were prescribed platform injectables. Furthermore, in the same study during follow-up of 3.9 years, only 55% of the patients used one DMT, while others switched to later lines of therapy. The main reasons for switching from platform therapies were poor tolerability or noncompliance, or refractory disease.¹⁸ Narula et al¹⁹ suggested that switching to a different first-line therapy or escalation to newer DMTs for patients with unmanageable adverse effects or poor tolerance or compliance is widely observed in recent practice. When cycling through first-line platform therapies is not beneficial, starting with second-line DMTs should be considered.¹⁸ This observation was supported by another retrospective

study conducted in an Italian pediatric MS population in which 85% of patients switched at least once during mean follow-up of 12.5 years. Of those who switched treatment, 46% were treated with interferon beta-1a, and the results of univariate analysis showed that choosing interferon beta-1a as the first line of treatment was one of the two variables correlated with a worse MS outcome.²⁰ In a prospective study assessing pediatric patients with clinically isolated syndrome and MS with follow-up of 3.5 years, 30.4% of those receiving first-initiated injectable therapies switched to a newer DMT.¹³

The present study showed that median time to discontinuation of first-initiated DMTs was less than 4 months. A report by the International Pediatric MS Study Group acknowledged that approximately 40% of children with MS discontinue treatment due to medication intolerance, adverse effects, or relapses, suggesting a need for improved treatment options.²¹ A study conducted in 12 outpatient practices participating in the US Network of Pediatric MS Centers (N = 1019) showed a lower discontinuation rate in patients treated with dimethyl fumarate and fingolimod compared with those taking other newer DMTs.¹³

Overall, there is a need for a better understanding of suboptimal response, safety, persistence-switching, and impact of treatment on quality of life specific to individual DMT use in the pediatric setting.

The present study further strengthens the existing literature evaluating these treatment outcomes in a large claims database across the United States and included participants irrespective of their MS phenotype, sex, and other demographic characteristics. It is important to acknowledge that the treatment landscape in adult patients with MS is evolving and may change over time, although no new DMTs apart from fingolimod

PRACTICE POINTS

- This study concluded that of 288 newly diagnosed pediatric patients (<18 years old) with MS, 188 (65.3%) were not treated within the first year of MS diagnosis.
- Most patients started with platform injectables (glatiramer acetate and interferon), and approximately one in three patients starting on their first disease-modifying therapy either discontinued or switched within 6 months of therapy initiation during follow-up.
- This study raises awareness of undertreatment, observed in this cohort, to encourage early treatment in pediatric MS.

have been recently approved for pediatric patients. Furthermore, considering that the prevalence of MS in the pediatric population is low, the sample included was representative of the US population (and geography) and provided interpretable results.

However, a few limitations of this study must be considered. First, the Truven Health MarketScan Commercial Supplemental Databases do not contain information on clinical measures of disease severity (eg, Expanded Disability Status Scale score, magnetic resonance imaging findings), and, therefore, such measures could not be incorporated to characterize the pediatric MS patient population. Another limitation of using a commercial claims database is that it does not capture reasons for delayed initiation of DMT or for discontinuation or switching of DMTs. Given that the prevalence of MS in the pediatric population is low and has limited follow-up time, these results should be interpreted considering the smaller sample size and as a short-term assessment of outcomes. The included population is small also because pediatric patients who were not continuously enrolled with medical and pharmacy benefits were excluded (60% of pediatric patients with MS lack continuous enrollment). Finally, the present study included only patients younger than 18 years who were covered by employer-sponsored commercial health plans. Therefore, the results may not be generalizable to other populations, such as uninsured patients. Future analyses on subgroups of pediatric patients by age in a larger sample with longer follow-up beyond a year are warranted.

In conclusion, this study shows that a considerable proportion of pediatric patients with MS remain undertreated in the United States. Approximately one in three patients on first-initiated DMT have early treatment failure (switching or discontinuation). Overall, based on these data, the study highlights the need for treating children and adolescents with MS with an optimal therapy for improvement. □

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References

1. Waldman A, Ghezzi A, Bar-Or A, et al. Multiple sclerosis in children: an update on clinical diagnosis, therapeutic strategies, and research. *Lancet Neurol*. 2014;13:936-948.
2. Benson LA, Healy BC, Gorman MP, et al. Elevated relapse rates in pediatric compared to adult MS persist for at least 6 years. *Mult Scler Relat Disord*. 2014;3:186-193.
3. Gorman MP, Healy BC, Polgar-Turcsanyi M, et al. Increased relapse rate in pediatric-onset compared with adult-onset multiple sclerosis. *Arch Neurol*. 2009;66:54-59.
4. Mikaeloff Y, Caridade G, Billard C, et al. School performance in a cohort of children with CNS inflammatory demyelination. *Eur J Paediatr Neurol*. 2010;14:418-424.
5. Chitnis T, Tenenbaum S, Banwell B, et al. Consensus statement: evaluation of new and existing therapeutics for pediatric multiple sclerosis. *Mult Scler*. 2012;18:116-127.
6. Ghezzi A, Banwell B, Boyko A, et al. The management of multiple sclerosis in children: a European view. *Mult Scler*. 2010;16:1258-1267.
7. Chitnis T, Arnold DL, Banwell B, et al. Trial of fingolimod versus interferon beta-1a in pediatric multiple sclerosis. *N Engl J Med*. 2018;379:1017-1027.
8. Kavaliunas A, Manouchehrinia A, Stawiarz L, et al. Importance of early treatment initiation in the clinical course of multiple sclerosis. *Mult Scler*. 2017;23:1233-1240.
9. Simone M, Chitnis T. Use of disease-modifying therapies in pediatric MS. *Curr Treat Options Neurol*. 2016;18:36.
10. Charlson ME, Pompei P, Ales KA, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373-383.
11. Young B, Waubant E, Lulu S, et al. Puberty onset and pediatric multiple sclerosis activity in boys. *Mult Scler Relat Disord*. 2019;27:184-187.
12. Langille MM, Islam T, Burnett M, et al. Clinical characteristics of pediatric-onset and adult-onset multiple sclerosis in Hispanic Americans. *J Child Neurol*. 2016;31:1068-1073.
13. Krysko KM, Graves J, Rensel M, et al. Use of newer disease-modifying therapies in pediatric multiple sclerosis in the US. *Neurology*. 2018;91:e1778-e1787.
14. MacAllister WS, Christodoulou C, Troxell R, et al. Fatigue and quality of life in pediatric multiple sclerosis. *Mult Scler*. 2009;15:1502-1508.
15. Wenten M, Richman S, Everage N, et al. Comorbid conditions and medication utilization among pediatric-onset multiple sclerosis patients in the United States. *Mult Scler*. 2015;23:83.
16. Suh K, Gorsh B, Prasla K, et al. Perceptions of multiple sclerosis and disease modifying therapies among currently untreated MS patients. *Value Health*. 2013;16:A105-A106.
17. Goodin DS, Reder AT, Ebers GC, et al. Survival in MS: a randomized cohort study 21 years after the start of the pivotal IFN β -1b trial. *Neurology*. 2012;78:1315-1322.
18. Yeh EA, Waubant E, Krupp LB, et al. Multiple sclerosis therapies in pediatric patients with refractory multiple sclerosis. *Arch Neurol*. 2011;68:437-444.
19. Narula S, Hopkins SE, Banwell B. Treatment of pediatric multiple sclerosis. *Curr Treat Options Neurol*. 2015;17:1-12.
20. Baroncini D, Zaffaroni M, Moiola L, et al. Long-term follow-up of pediatric MS patients starting treatment with injectable first-line agents: a multicentre, Italian, retrospective, observational study. *Mult Scler*. 2019;25:399-407.
21. Wassmer E, Chitnis T, Pohl D, et al. International Pediatric MS Study Group Global Members Symposium report. *Neurology*. 2016;87:S110-S116.