Treatment Failure in patients with multiple sclerosis initiating frequently used first line therapies

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Disclosures

This study was sponsored by Novartis Pharmaceuticals Corporation.

Chinmay Deshpande and **Fei Yang** are employees of Novartis Pharmaceuticals Corporation.

Wang Mengru is an employee of KMK Consulting, Inc. and works as a consultant to Novartis Pharmaceutical Corporation.

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The final responsibility for the content lies with the authors.

Background and objective

- Currently, more than 18 disease modifying therapies (DMTs) are approved for the treatment of multiple sclerosis (MS) by the United States Food and Drug Administration (US FDA).

- Despite the availability of multiple DMTs, interferons/glatiramer acetate (IFN/GA) and dimethyl fumarate (DMF) are still the most frequently used therapies to treat multiple sclerosis (MS) in the US.

- The role/benefit of newer and more efficacious DMTs in the early management of MS is yet to be well defined, which leads clinicians to face considerable uncertainty regarding the best treatment plan for these patients.

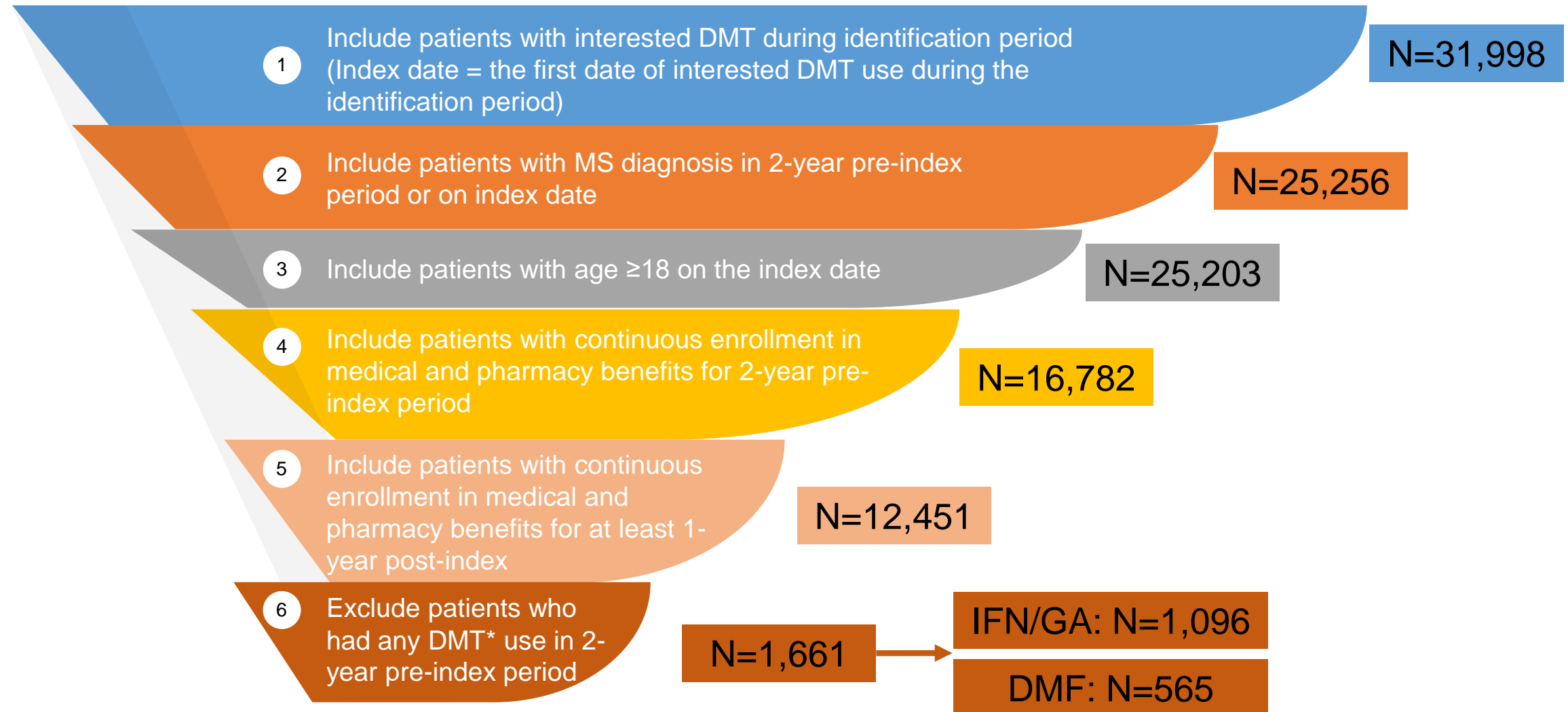| **Objective**	**To evaluate treatment patterns and disease breakthrough for patients initiating IFN/GA/DMF as first-line therapies to determine if there is an unmet need for more effective agents to be used first-line.**

Methods: Study design, outcomes, and statistical analysis

- Newly diagnosed patients (age ≥18) with ≥1 DMT claims of IFN/GA/DMF from January 2016-March 2018 were retrospectively identified using a large US administrative claims database (IBM® MarketScan® Database).

- The date of the first MS DMT claim was defined as the index date and patients were followed for one year.

- 24 months of continuous health plan enrollment prior to and 12 months after the index date were required.

- Outcomes were evaluated as a combined DMT (IFN/GA or DMF) group, and by individual DMTs (IFN vs. GA vs. DMF).

Study design

Identification period

03/31/2019

1/1/2014   1/1/2016   03/31/2018

Baseline period (24 months)

Follow-up period (12 months)

Study period

Disease breakthrough was defined as occurrence of relapse (characterized via a validated claims algorithm) during the treatment period
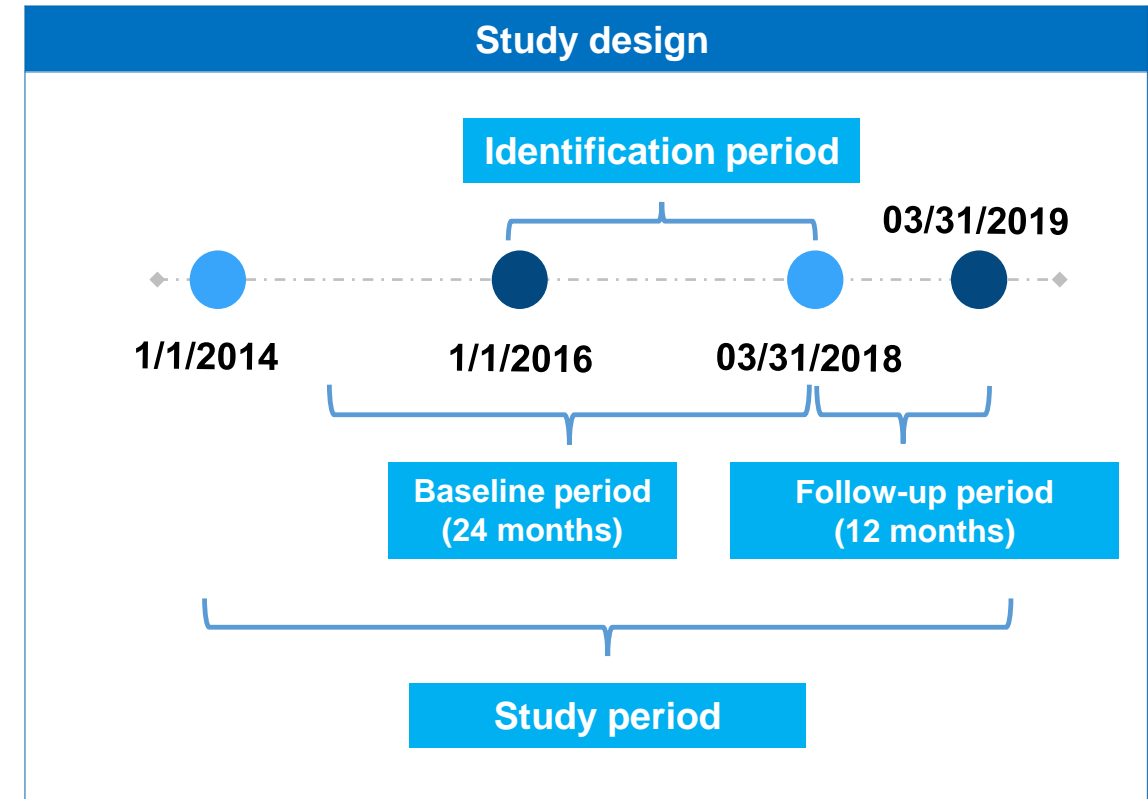
Treatment switch was defined as changing from initial therapy to another DMT (within 60 days) and discontinuation was defined as no DMT use for at least 60 days after stopping the initial DMT

DMF: Dimethyl fumarate; DMT: Disease modifying therapy; GA: Glatiramer acetate; IFN: Interferon

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Patient flow

1. Include patients with interested DMT during identification period (Index date = the first date of interested DMT use during the identification period)
   N=31,998

2. Include patients with MS diagnosis in 2-year pre-index period or on index date
   N=25,256

3. Include patients with age ≥18 on the index date
   N=25,203

4. Include patients with continuous enrollment in medical and pharmacy benefits for 2-year pre-index period
   N=16,782

5. Include patients with continuous enrollment in medical and pharmacy benefits for at least 1-year post-index
   N=12,451

6. Exclude patients who had any DMT* use in 2-year pre-index period
   N=1,661 → IFN/GA: N=1,096
   DMF: N=565

*DMTs other than IFN/GA/DMF could have been used but were excluded in line with the study objective
DMF: dimethyl fumarate; DMT: disease modifying therapy; GA: glatiramer acetate; IFN: interferon

Baseline demographics

- For the overall cohort (IFN/GA/DMF), the annualized relapse rate (ARR*) for patients in the 12 month pre-index period was 0.41 (0.61).

- In terms of disability level, about 60% of patients had moderate or severe disability.

- Proxy disability level was assessed using MS symptoms (mild, moderate, severe) based on Berkovich et al. 2019[1] as defined below:

  - Mild disability level is defined as having only one functional system (FS) with severity level=1.

  - Moderate disability level is defined as having more than 1 FS with severity level=1, or having any EDSS-related symptoms with severity level=2.

  - Severe disability level is defined as having any EDSS-related symptoms with severity level=3

	Overall (IFN/GA/DMF) N=1,661	IFN/GA N=1,096	DMF N=565
Age, years			
Mean (SD)	44.8 (11.8)	44.8 (11.9)	44.9 (11.6)
Sex, n (%)			
Female	1,257 (75.7%)	838 (76.5%)	419 (74.2%)
United States Region: N (%)			
Northeast	375 (22.6%)	243 (22.2%)	132 (23.4%)
North Central	335 (20.2%)	236 (21.5%)	99 (17.5%)
South	698 (42.0%)	464 (42.3%)	234 (41.4%)
West	252 (15.2%)	152 (13.9%)	100 (17.7%)
Unknown	1 (0.1%)	1 (0.1%)	0 (0.0%)
Insurance Type: n (%)			
Fee for service	1,458 (87.8%)	950 (86.7%)	508 (89.9%)
HMO and POS capitation	191 (11.5%)	137 (12.5%)	54 (9.6%)
Unknown	12 (0.7%)	9 (0.8%)	3 (0.5%)
With at least one relapse, n (%)	662 (39.9%)	431 (39.3%)	231 (40.9%)
ARR in 1-year pre-index			
Mean (SD)	0.41 (0.61)	0.42 (0.63)	0.41 (0.59)
Proxy disability level[1], n (%)			
No-EDSS related symptoms	307 (18.5%)	200 (18.2%)	107 (18.9%)
Mild	383 (23.1%)	260 (23.7%)	123 (21.8%)
Moderate	641 (38.6%)	426 (38.9%)	215 (38.1%)
Severe	330 (19.9%)	210 (19.2%)	120 (21.2%)

[1]Berkovich R, et al. *Multiple Sclerosis Journal*. 2019; 25: 113-114
*An MS relapse was defined using a well-established algorithm as a claim with an MS diagnosis code (ICD-9-CM code 340 or ICD-10 G35) in the primary position at any time during an inpatient hospitalization or a claim with an MS diagnosis code in the primary or secondary position in an outpatient setting in addition to a pharmacy or medical claim for a qualifying corticosteroid on the day of or within 7 days after a visit;
DMF: Dimethyl fumarate; DMT: Disease modifying therapy; GA: Glatiramer acetate; IFN: Interferon

Discontinuation and Switching

Approximately 43.4% of patients experienced treatment failure* within one year of initiation
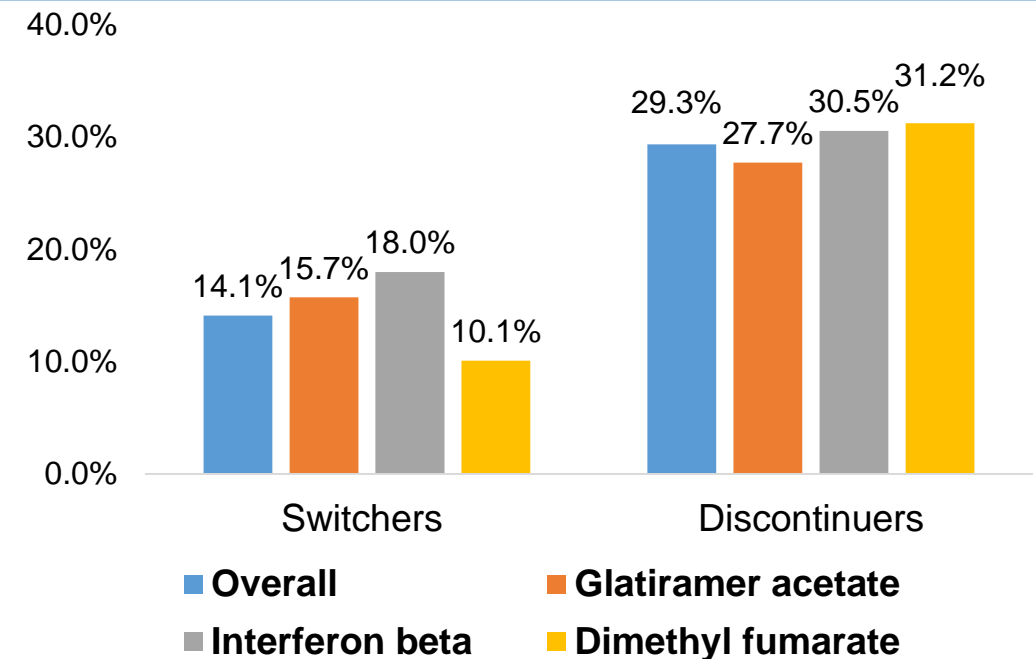
Discontinuation

- Overall, 29.3% of the patients starting IFN/GA or DMF discontinued treatment within one year of initiation.

- Median time to discontinuation among these patients was 4.8 months.

Switching

- Approximately 14.1% of the patients switched to another DMT from IFN/GA or DMF within one year after initiation.

- Median time to switch to second line therapy was 5.6 months.

Proportion of patients who discontinued or switched to another therapy within one year of initiation

Bar chart legend:
- **Overall** (blue)
- **Glatiramer acetate** (orange)
- **Interferon beta** (grey)
- **Dimethyl fumarate** (yellow)

Switchers: 14.1%, 15.7%, 18.0%, 10.1%
Discontinuers: 29.3%, 27.7%, 30.5%, 31.2%

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*Treatment failure was defined as discontinuation or switching within 1 year of initiation
DMF: Dimethyl fumarate, DMT: Disease modifying therapy; GA: Glatiramer acetate; IFN: Interferon; IQR: Inter quartile range, SD: Standard deviation

Disease breakthrough
No relevant change in ARR was observed after one year of treatment with first line DMTs

- 28% of the patients initiating IFN/GA or DMF experienced at least 1 relapse over a follow-up period of 1 year.

- Patients experienced relapse within approximately median 5 months of treatment initiation with IFN/GA or DMF.

- There was no reduction in annualized relapse rate (ARR) in the combined DMT cohort (IFN/GA or DMF therapy) [ARR for 1-year prior to initiation = (0.41) and 1 year post-initiation = (0.42)].
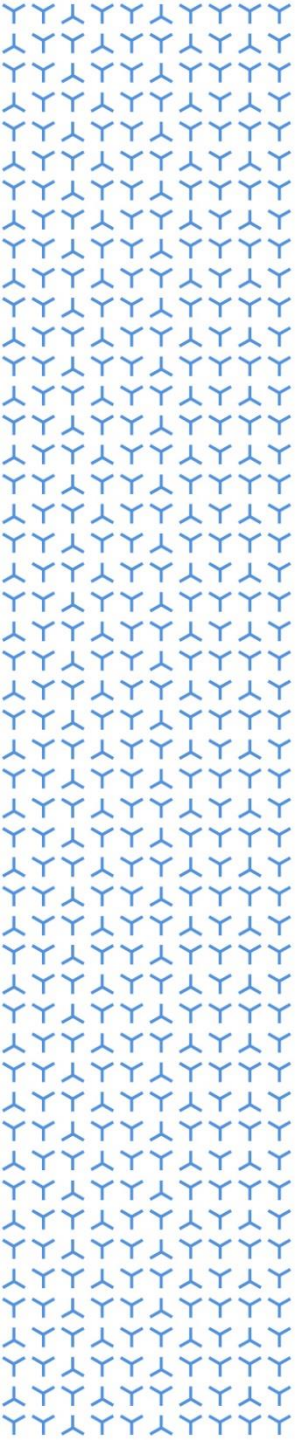
Proportion of patients with at least one relapse over a follow-up of one year

Bar chart:
- Overall: 28.2%
- Glatiramer acetate: 31.7%
- Interferon beta: 26.6%
- Dimethyl fumarate: 23.6%

DMF: Dimethyl fumarate; DMTs: Disease modifying therapies; GA: Glatiramer acetate; IFN: Interferon
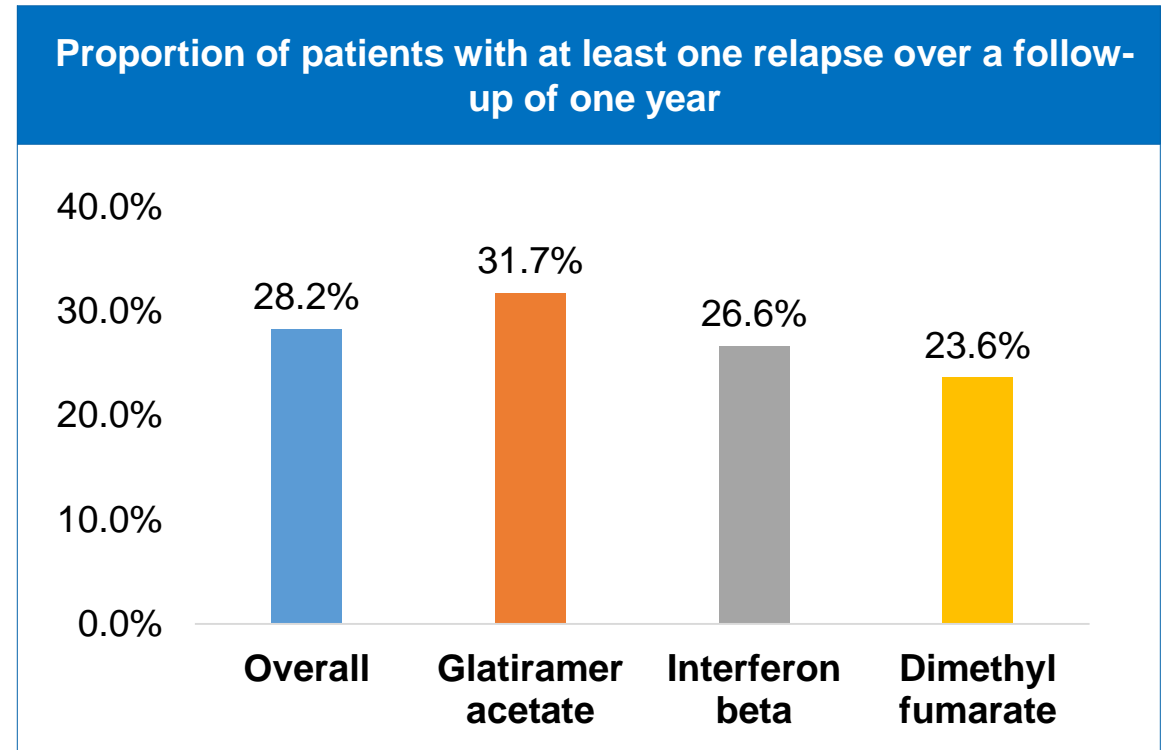
Limitations

- The IBM® MarketScan® claims database do not contain clinical measures of disease severity (e.g. EDSS, MRI), and therefore, proxy measures were used for capturing disability/relapses.

- The pharmacy prescription fill claim is a proxy measure of patients' drug utilization. Patients may or may not use medication as prescribed after filling a prescription. Therefore, dates of treatment initiation and discontinuation were approximate.

- Although IBM® Marketscan® is considered a nationwide database, it primarily includes employer sponsored patients, so the data might not be generalizable for uninsured and government insured populations.

EDSS: Expanded disability status scale; MRI: Magnetic resonance imaging

Conclusions

- The most frequently used first-line DMTs (IFN/GA/DMF) showed considerable treatment failure (discontinuation/switching) and sub-optimal benefit (disease breakthrough) in a real-world setting. This indicates that there is still an unmet need for an early high efficacy therapy which may be further investigated.

- Given the current results and emerging evidence on early use of high efficacy therapy, providers might want to consider alternatives in an early MS population in the appropriate clinical context.

ARR: Annualized relapse rate; DMTs: Disease modifying therapies; MS: Multiple sclerosis

Thank you