Introduction:

Multiple sclerosis (MS) is an autoimmune disorder affecting the central nervous system. According to The National MS Society, there are nearly a million people in the United States of America living with MS [6]. Patients diagnosed with MS experience a variety of symptoms including, but not limited to, pain, fatigue, cognitive dysfunction, and myopathy. These symptoms greatly disrupt patient's quality of life and activities of daily living. Currently, MS has no cure, and the standard of care is implementation of early and effective disease modifying therapy. Selecting the disease modifying therapy should be based on patient's preference, risk for adverse effects, tolerability, effectiveness and cost. There are a number of options for disease modifying medications, including injectable medications such as interferon beta-1a, peginterferon beta-1a, and glatiramer acetate, oral medications such as fingolimod, dimethyl fumarate, and siponimod, and infusion medications such as alemtuzumab, ocrelizumab, and natalizumab.

Dimethyl fumarate is an oral disease modifying therapy used in the treatment of relapsing forms of MS, including clinically isolated syndrome, relapsing–remitting disease, and active secondary progressive disease [3]. Dimethyl Fumarate is the number one oral prescribed drug for relapsing MS in the United States since September 2013 [7]. In the Phase III DEFINE and CONFIRM clinical studies, dimethyl fumarate was proven efficacious in relapsing MS by improving neurologic outcomes through decreasing relapse and disability rates and new active MRI lesions [1,2]. While dimethyl fumarate has improved outcomes in MS, the medication has a high incidence of adverse events leading to drug discontinuation and drug non-adherence.

In the Phase III DEFINE clinical study, common adverse events reported by patients taking dimethyl fumarate compared to placebo are gastrointestinal (GI) side effects such as diarrhea (15%), abdominal pain (11%), nausea (13%), and flushing (38%) in patients taking twice daily 240mg dimethyl fumarate. These adverse events are common in the first month and decrease as therapy progressed. Of the 16% of patients that discontinued therapy in the DEFINE clinical study, for the twice daily 240 mg dimethyl fumarate group, 2% were discontinued due to flushing and 5% were discontinued due to GI adverse events [1].

In the Phase III CONFIRM clinical study, common adverse events reported by patients taking dimethyl fumarate 240 mg twice daily compared to placebo and glatiramer acetate were flushing (35%), diarrhea (13%), abdominal pain (10%), and nausea (11%). The incidences of the adverse events was the highest in the first months and decreased as therapy progressed. Of the 12% of patients that discontinued therapy in the CONFIRM clinical study, for the twice daily dimethyl fumarate group, 4% were discontinued due to flushing and 2% were discontinued due to nausea and diarrhea [2].

The two primary concerns for adverse events are flushing and GI events. As a result, the package insert for dimethyl fumarate recommends oral administration with food, pre-medicating with non-enteric coated aspirin 325 mg 30 minutes prior, and a standard titration schedule of 120 mg twice daily for 1 week prior to increasing to 240 mg twice daily as the maintenance dose to help reduce GI events and flushing. The mechanism behind the adverse events of GI events and

flushing can be explained through dimethyl fumarate's metabolism. Dimethyl fumarate is metabolized into two major metabolites, monomethyl fumarate and methanol. Methanol is a GI irritant, which can cause the adverse events of nausea, diarrhea, and abdominal pain. Monomethyl fumarate binds to the nicotinic acid receptor *in vitro*. By binding to the nicotinic acid receptor, monomethyl fumarate can cause flushing [3].

In a Delphi study, a survey was taken on clinician management strategies for GI side effects and flushing from dimethyl fumarate. The study showed a consensus of management by administering with food, slow titration, dose reduction, and use of symptomatic therapies. In the study, survey responders agreed (88%) that a slow dose titration was effective in reducing the GI side effects. Survey responders varied on the slow titration dosage methods. Some of the titration methods included less than 2-week, 4-week, and 6-week titration. [4].

There is currently limited data and studies on the efficacy of alternate titration schedules. However, *O'Gorman, et al.* studied the efficacy of a 3-week titration of dimethyl fumarate on the reduction of the incidence and severity of GI events and flushing over an 8-week period. Seventy-nine percent of patients had GI adverse events during weeks 1 to 4 and 61% patients still had GI adverse events during weeks 5 to 8. Ninety-eight percent of patients had flushing weeks 1 to 4 and 85% of patients had flushing weeks 5 to 8. No subjects discontinued drug because of flushing, but 2% of subject discontinued dimethyl fumarate because of GI adverse events. This 3-week slow-titration of dimethyl fumarate was shown to be non-effective [5].

At a specialty MS clinic at a large academic medical center, medical providers initiated a 3-week slow titration schedule as a standard regimen for the tolerability management strategy for dimethyl fumarate. As part of the treatment plan, patients receive 120 mg daily during week 1, then 240 mg daily during week 2, then 120 mg in the morning and 240 mg in the evening during week 3, then 240 mg twice daily during the remainder of the treatment as the maintenance dose. This study aims to assess the efficacy of a 3-week slow titration period in decreasing the risk and incidence of GI adverse events and flushing when compared to the standard titration period recommended by the package insert. The hypothesis is that a slow titration schedule will be effective in reduction of adverse events and improve tolerability. The results of this study will be impactful as it will contribute to a gap in knowledge regarding the appropriate dosing schedule for the treatment of patients with MS taking dimethyl fumarate.

Methods:

This study will be conducted at a large medical center with a specialty pharmacy and clinic. This is a retrospective chart review of patients who were treated at the MS clinic from July 2017 to July 2019, received a prescription for dimethyl fumarate, and completed a 3-week slow titration. As part of the patient visit, patients reported adverse events to the medical provider or clinical pharmacist. Electronic medical records and pharmacy documentation will be reviewed to collect information about adverse events.

Data analysis:

Fisher's exact test was used to compare the proportion of adverse events between patients who received 3-week slow titration of dimethyl fumarate versus twice daily dosing of dimethyl fumarate in DEFINE and CONFIRM trials. The risk difference each adverse event type for the slow titration study was additional calculated from the proportions in each study and reported along with 95% confidence intervals (95% CI). All statistical tests were two-sided with an alpha level set at 0.05 for statistical significance. All statistical analyses were performed using SAS 9.4.

Results and Discussion:

In this study, a 3-week slow titration was compared to twice daily dosing of dimethyl fumarate in DEFINE and CONFIRM trials. The differences in the proportion of adverse events were reported from months 0 to 3 in both the slow titration and clinical trials. A slow titration of dimethyl fumarate may not be effective in reducing adverse events. In the 3-week slow titration in comparison to twice daily dosing from CONFIRM AND DEFINE, the 3-week slow titration had higher rates of abdominal pain, nausea, and flushing, but lower rates of diarrhea (Table 2).

In comparing the reasons for discontinuations, the 3-week slow titration is not able to be compared to CONFIRM and DEFINE trials as the 3-week slow titration rates are from over 3 months, while CONFIRM and DEFINE trials are discontinuation rates over two years of the study. However, trends in discontinuation rates can be compared. Discontinuation rates are similar, however patients in the slow titration reported more GI discontinuations as compared to the CONFIRM and DEFINE trials. CONFIRM and DEFINE trials reported other reasons for discontinuation, such as MS relapse, but flushing and GI discontinuations are more common (Table 3).

In this study, 28 of 38 patients received dimethyl fumarate from outside pharmacies, so there is uncertainty of the type of medication education received before beginning therapy, therefore there is a potential barrier of patients not having proper medication consultation on medication administration and adverse event management. Even after proper medication education, patients may not be taking preventative measures to stop adverse events. During chart review, researchers realized providers are using medications to help with adverse events, such as aspirin, diphenhydramine, pantoprazole, and ranitidine (Table 4). In the package insert for dimethyl fumarate, only aspirin is recommended for symptomatic management. Only 5 of the 19 patients who reported flushing used aspirin as a premedication. There was a missed opportunity for the clinical pharmacist to make a medication intervention.

Limitations:

This study may not be adequately powered to detect a difference in the incidence of adverse events in the titration protocol compared to the clinical trials. In the 3-week slow titration, there was 38 patients enrolled in comparison to over 700 patients in the clinical trials. The study is not able to be effectively compared to clinical trials to determine a difference due to the small study sample size. This retrospective chart review's documentation is not as robust in comparison to

the clinical trials. In the clinical trials, researchers are calling patients and obtaining the type of side effects and severity of side effects as in this study, researchers are relying solely on patient documentation.

The patients in the retrospective chart review who were initiated on dimethyl fumarate used a slow titration schedule, therefore no data of a one-week titration is available to compare the study results to. This is a two part limitation. The first part of this limitation is in the clinical trials, patients received twice daily dosing without a titration, therefore we have no data of a one week titration to compare the 3-week titration too. Also, at the MS center all patients are started on slow titration schedule, therefore we do not have our own subset of patients on a one week titration to compare the three week titration data too.

Conclusion:

In conclusion, a 3-week slow titration of dimethyl fumarate may not be effective in reduction of adverse events and improvement in patient tolerability in comparison to FDA approved twice daily dosing.

Future direction: Pharmacists should continue to educate patients on how to administer dimethyl fumarate and the importance of pre-medication. There is a plan to present 3-week slow titration results to the MS center for further evaluation and use of a slow titration schedule. In 2019, diroximel fumarate, a derivative of dimethyl fumarate, was approved. Diroximel fumarate is metabolized differently from dimethyl fumarate. Diroximel fumarate is metabolized to monomethyl fumarate and 2-hydroxyethyl succinimide, which is shown to have decreased GI adverse events. Medical Providers and patients will use shared decision making on whether to begin patients on dimethyl fumarate or diroximel fumarate.

References

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Appendix:

Baseline Demographics:

Table 1. Cohort characteristics (n=38)	
Age, years	
Median [IQR]	45 [33-51]
Min, Max	(24, 79)
Gender	
Female	26 (68.4%)
Male	12 (31.6%)
Race	
African American	1 (2.6%)
Asian	1 (2.6%)
Native Hawaiian / Other Pacific Islander	1 (2.6%)
Unknown	1 (2.6%)
Other	13 (34.2%)
White	21 (55.3%)
Previous DMT use	29 (76.3%)
Time since MS diagnosis, years	
Mean	7.3
Prescriptions Filled at USC Specialty Pharmacy	10 (26.3%)

Results:

Table 2. **Differences in the proportion of adverse events in months 0-3**				
Adverse Event	3-week slow titration (n=38)	DEFINE/CONFIRM Trials dimethyl fumarate BID (n=769)*	Risk Difference from DEFINE/CONFIRM (95% CI)	p-value
Diarrhea	2 (5.3%)	9%	-3.7% (-11.1%,3.7%)	0.57
Abdominal pain	5 (13.2%)	7%	6.1% (-4.8%,17.0%)	0.19
Nausea	7 (18.4%)	9%	9.5% (-3.0%,21.9%)	0.08
Flushing	19 (50.0%)	37%	12.9% (-3.3%,29.2%)	0.12
Other┼	14 (36.8%)	NA	NA	NA

*Back calculated N= 69, 69, 285, and 54 for nausea, diarrhea, flushing, and abdominal pain, respectively.
┼ indigestion, vomiting, and itching

Table 3. Reasons for discontinuations	**3-week slow titration (n=38)**	**CONFIRM (n=359)**	**DEFINE (n=410)**
Total discontinuations	7 (18%)	44 (12%)	65 (16%)
GI discontinuations	6 (13%)	7 (2%)	21 (5%)
Flushing discontinuations	1 (3%)	14 (4%)	10 (2%)
Other	1 (3%)	23 (6%)	34 (9%)

Table 4. Symptom Management			
Medication	3-week slow titration (n=38)	Prophylactic	Treatment
Aspirin	6 (15.8%)	X	
Diphenhydramine	3 (7.9%)		X
Pantoprazole	1 (2.6%)		X
Ranitidine	1 (2.6%)		X