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Real-life persistence and tolerability with dimethyl fumarate

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ABSTRACT

Background: Dimethyl fumarate (DMF) has been registered for the treatment of relapsing-remitting multiple sclerosis (RRMS). Differences in tolerability between multiple sclerosis clinics in patients treated with DMF has not been examined.
Aim: We examined real-world tolerability to DMF, and also compared adherence data between two MS clinics.
Methods: Adverse events (AE), discontinuation rates, and causes of discontinuation were investigated.
Results: 253 patients participated in this retrospective study. In the total cohort, 27.7% of the patients discontinued DMF. Higher rate of discontinuation was associated with higher number of previous disease modifying treatments ($p < 0.001$). Reasons for discontinuation were primarily flushing (15%) and gastrointestinal AEs (51%). Grade III lymphopenia was detected only in 6 cases (2.4%). We observed differences between the two clinics: discontinuation because of AEs was different (Odds ratio 6.13, 95% CI: 3.0–12.7, $p < 0.001$), the mean treatment duration also differed (305.3 ± 186.3 vs 140.5 ± 114.4 days, $p < 0.001$), and dissimilarities in adherence were mainly related to flushing, gastrointestinal AEs, and consideration of lymphopenia ($p < 0.0001$). Better adherence was associated with prospectively planned management of gastrointestinal AEs and flushing.
Conclusion: Adherence in real-life was similar to pivotal trials. Differences in discontinuation rates at two MS clinics underline importance of AE management.

1. Introduction

Efficient patient management and adherence to medicines is critical to ensure efficacy of therapy. Even in chronic progressive diseases such as multiple sclerosis (MS), adherence to disease modifying treatments (DMTs) is often compromised and reported as low as 12–59% (Menzin et al., 2013).

Adherence in MS depends on patients' attitude towards their disease, understanding the general concept of disease modifying treatments interfering with disease activity, and their expectation towards the specific treatment prescribed. Non-adherence is associated with higher relapse rate and significant health care expenses in MS (Menzin et al., 2013; Steinberg et al., 2010; Tan et al., 2011). The most common reasons for non-adherence are adverse events, forgetfullness, costs, the number of drugs prescribed and patients experiencing lack of disease activity. Importantly, the patients' attitude towards treatment is influenced by interaction with health care professionals. Thus, the patients' motivation and compliance may be affected positively by the treating MS physicians and MS nurses (Jongen et al., 2016; Theodore Phillips et al., 2015; Thomas et al., 2016).

Delayed release dimethyl fumarate (DMF, Tecfidera®) is an oral agent registered for the treatment of patients with relapsing-remitting multiple sclerosis (RRMS). The clinical phase 3 trials demonstrated significant clinical and radiological treatment benefits of DMF 240 mg twice daily with a relapse rate reduction of 53% and 44% over placebo, and 38% relative risk reduction of progression over placebo (Fox et al., 2012; Gold et al., 2016, 2012). The rate of adverse events (AE) in these two trials was similar in all treatment groups, reporting mild or moderate flushing and gastrointestinal (GI) adverse events (36% and 42%, respectively). In the phase 3 clinical trials, flushing led to discontinuation of DMF in 3% of cases, and GI-events were the cause of discontinuation in 4% of the patients. The phase 3 and phase 4 follow-up trials furthermore established that the GI-events and flushing were transient, i.e. the incidences were highest during the first month of treatment and declined in the months thereafter (Thomas et al., 2016; Fox et al., 2012; Gold et al., 2016, 2012). Patients may also prefer oral treatment instead of injectables, and quality of life seems to improve on DMF compared to daily subcutaneous injections (Kita et al., 2014;

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Table 1
Demographics and previous disease modifying treatments.

Clinic	Number of patients	Ratio male/ female	Age[a]	Treatment naïve	Previous 1st line[b]	Previous 2nd line[c]
#1	103	24/79	40.2 ± 10.7	18	62	23
#2	150	53/97	40.9 ± 10.9	56	87	7

[a] Mean ± SD.
[b] Glatiramer acetate, interferon beta, teriflunomide.
[c] Fingolimod and natalizumab

Vermersch et al., 2016).

As non-adherence is associated with higher risk of relapses and socioeconomic burden, improving the strategies for management of AEs may be important to clinical outcomes. This paper presents the real-life clinical experience with tolerability and adherence during DMF treatment. The paper also demonstrates that adherence can be affected by management-strategies of AEs.

2. Materials and methods

2.1. Patients and study design

DMF has been commercially available in Denmark since March 2014. We retrospectively reviewed patients' data at two major MS clinics in Denmark. Both clinics are responsible for the care of roughly 1100–1500 MS patients. Patients were enrolled in this retrospective analysis if they started treatment between March 2014 and November 2015. Age, gender, previous treatments, adverse events (AEs), laboratory results, treatment duration, ratio and reasons of discontinuation were assessed. The study was approved by the Danish Patient Safety Authority (3-3013-1622/1) and the Danish Data Protection Agency (16/11931).

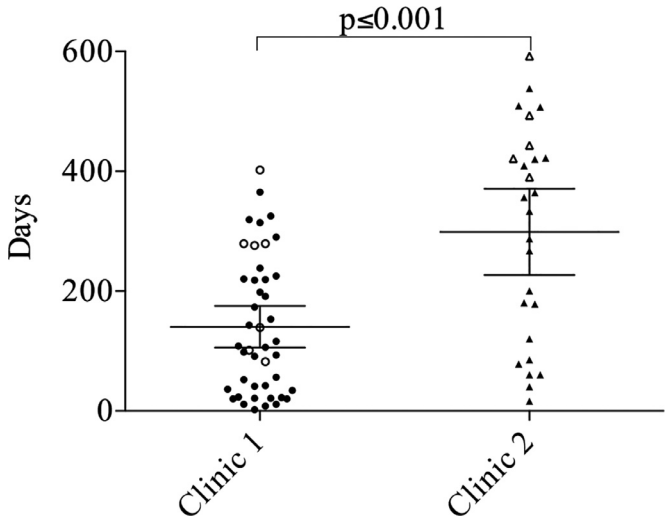

Fig. 2. Proportions of patients, who continued and discontinued dimethyl fumarate.
A: The percentage of patients who continued and discontinued treatment at Clinic 1 (n = 103) and Clinic 2. (n = 150).
B: The percentage of adverse events excluding pregnancy and relapse that resulted in discontinuation of DMF at clinic 1 (n = 35) and clinic 2 (n = 12).

2.2. Lymphocyte measurements and calculation of biological variation

Lymphocyte counts were measured at Sysmex XN-9000 according to

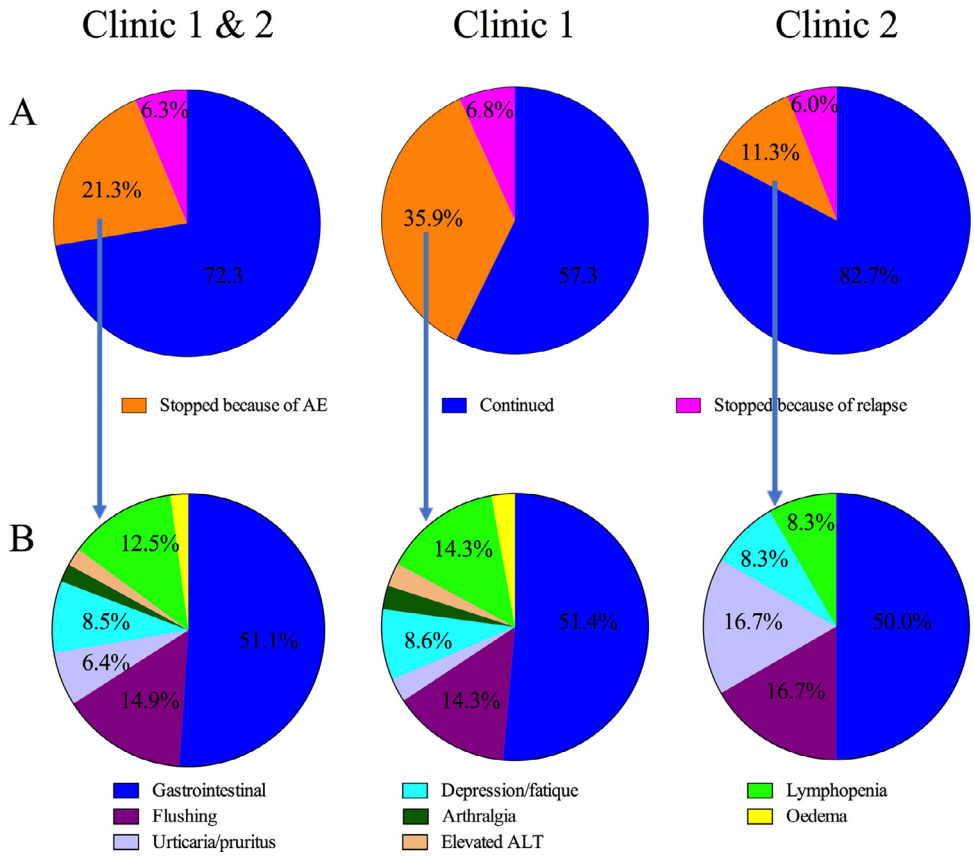

Fig. 1. Treatment duration among patients, who discontinued dimethyl fumarate.
Clear circles or triangles indicate discontinuation due to relapse. Whiskers indicate mean value and standard deviation.