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Clinical Observations

Oral Dimethyl Fumarate in Children With Multiple Sclerosis: A Dual-Center Study

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ABSTRACT

BACKGROUND: First-line injectable therapies for multiple sclerosis in children may be ineffective or not well-tolerated. There is therefore an urgent need to explore oral medications for pediatric multiple sclerosis. We review our dual-center experience with oral dimethyl fumarate. **METHODS:** This study was a retrospective review of children 18 years of age or less with multiple sclerosis treated with dimethyl fumarate at Yale University and the University of Colorado. Clinical, demographic, and magnetic resonance imaging parameters were analyzed. **RESULTS:** We identified 13 children treated with oral dimethyl fumarate for a median of 15.0 months (range, 1 to 25). Dimethyl fumarate was utilized as first-line therapy in five children (38%). Ten children (77%) tolerated dose escalation to the usual adult dose of 240 mg twice daily. Nine children had ≥12 months of follow-up on treatment. Eight of nine (89%) displayed stabilized or reduced relapse rates and disability scores on treatment. Nine children underwent brain magnetic resonance imaging performed after 12 or more months of therapy. New T2 lesions were observed in three children (33%), one of whom had been nonadherent to treatment. Common side effects included facial flushing (8/13, 62%), gastrointestinal discomfort (7/13, 54%), rash (3/13, 23%), and malaise (2/13, 15%). Three children (23%) discontinued treatment because of side effects. No patients displayed laboratory abnormalities including lymphopenia or abnormal liver transaminases. There were no reported infections. **CONCLUSIONS:** Oral dimethyl fumarate appears to be safe and generally well tolerated in children with multiple sclerosis. Formal clinical trials to evaluate efficacy are ongoing.

Keywords: multiple sclerosis, oral therapy, dimethyl fumarate, Expanded Disability Status Scale

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Introduction

Pediatric multiple sclerosis (MS) is being increasingly recognized, with approximately 2% to 10% of adult patients reporting their first symptoms before age 18 years.[1-3] As compared with adults, children with MS experience more frequent relapses early in the disease course, highlighting the importance of early initiation of disease-modifying therapies.[4]

Conventional first-line treatments for pediatric MS include interferon alpha, interferon beta, and glatiramer acetate (all injectable therapies). Although there have been no formal randomized clinical trials for these agents in children, studies support their safety and modest efficacy in children with MS and their use has been supported by international consensus statements.[5] Some children, however, continue to have frequent relapses despite these first-line therapies or are either unable or unwilling to comply with the required injections. There is therefore an urgent need to explore alternative oral medications that may have greater efficacy and tolerability in this age group.

Dimethyl fumarate (Tecfidera, Biogen Idec) is an oral medication approved for first-line use in adults with relapsing-remitting MS. Preclinical studies suggested that dimethyl fumarate (DMF) has both anti-inflammatory and cytoprotective properties likely mediated via activation of the nuclear factor (erythroid-derived 2)-like 2 transcriptional

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TABLE 1.
Patient Characteristics

Number of patients	13
Median age at first symptoms in years (IQR)	13.08 (2.83)
Median disease duration before treatment in years (IQR)	1.25 (2.92)
Sex (%)	
Boys	4 (30.77)
Girls	9 (69.23)
Self-reported ethnicity (%)	
Caucasian	8 (61.54)
Non-Caucasian	5 (38.46)
Disease subtype at first use (%)	
RRMS	10 (76.92)
CIS	3 (23.08)
Median EDSS (IQR)	1 (0)
Prior DMT use (%)	8 (61.54)
Glatiramer acetate	5
Interferon beta 1a	2
Interferon beta 1b	1
Natalizumab	2
Median duration of treatment with dimethyl fumarate in months (IQR)	15.00 (11)

Abbreviations:
CIS = Clinically isolated syndrome
DMT = Disease-modifying therapy
EDSS = Expanded Disability Status Scale
IQR = Interquartile range
RRMS = Relapsing-remitting multiple sclerosis

pathway.[6] This pathway plays a role in the cellular response to oxidative stress. DMF is generally administered twice daily with dose escalation to the target maintenance dose of 240 mg twice daily after one week. DMF has been shown to reduce both relapse rates and magnetic resonance imaging (MRI) lesion accrual in two large phase 3 studies conducted in adult patients with MS.[7,8] The safety, efficacy, and tolerability of DMF in children have not previously been reported. Here, we present our dual-center experience with oral DMF in children with MS.

Methods

We performed a retrospective analysis of children with relapsing-remitting MS treated with at least one dose of DMF between April 1, 2013, and August 1, 2015. All children were followed at the Yale MS Center, the Yale New Haven Hospital, the University of Colorado, or the Colorado Children's Hospital. Clinical data were obtained at each center by chart review using a standardized data collection tool.

Demographic data collected included age, sex, and ethnicity. We recorded the dosing regimen and total dose administered for all participants. We recorded annualized relapse rates in the year before, during, and after therapy, as well as all reported side effects and laboratory results. All children had a baseline complete blood count and evaluation of serum liver transaminases. Follow-up blood tests were performed according to institutional guidelines, but all children had a complete blood count at least every six months and serum transaminases checked at least annually. Expanded Disability Status Scale (EDSS) was recorded for all participants. An experienced pediatric MS neurologist (N.M. or T.S.) quantified the number of T2 and gadolinium-enhancing T1 brain MRI lesions using a standardized predefined scoring template that included the total number of T2 lesions and the number of gadolinium-enhancing lesions for each participant at baseline and serial time points. We obtained internal review board approval at each site as required.

We report medians with either range or interquartile range for continuous variables and frequency (percentage) for categorical variables. We used SAS statistical software v9.3 (SAS Institute Inc, Cary, NC).

Results

Participants

Baseline participant characteristics are summarized in Table 1. We identified 13 patients who were treated with at least one dose of DMF. There were more girls (9/13, 69%) than boys (4/13, 31%) and more Caucasian (8/13, 62%) than non-Caucasian (5/13, 38%) children treated. The majority of children (10/13, 77%) met formal MacDonald 2010 criteria for MS, whereas the remaining children (3/13, 23%) were treated following a single attack of neurological symptoms consistent with a diagnosis of clinically isolated syndrome.[9] The majority of children (8/13, 62%) had previously been treated with at least one other disease-modifying therapy, whereas DMF was used as a first-line agent in five children (38%). Twelve children (92%) had at least one relapse or new T2 brain MRI lesions in the year before DMF therapy. Nine children (69%) were tested for JC virus before commencing therapy and four of nine (44%) were initially positive.

Dosage and administration

Ten children (77%) tolerated dose escalation from 120 mg twice daily to 240 mg twice daily after one week. The remaining three children did not tolerate a dose above 120 mg twice daily. The median duration of therapy was 15.0 months (range, 1 to 25).

Response to treatment

Before treatment, children had a median of 1.0 relapse per year (range, 0-2). Nine children received at least 12 months of therapy, and in these nine children annualized relapse rate fell to a median of 0.6 (range, 0-1; Figure). Only one child treated for at least 1 year had an increased relapse rate following DMF. This child was an 11-year-old boy reporting treatment compliance at full dose who had already received greater than 36 months of natalizumab treatment before commencing DMF.

The pretreatment median EDSS in all children was 1.0 (range, 0-3). EDSS was stable or decreased in eight of nine children (89%) treated for at least 1 year (Figure). The one child with an increase in EDSS reported compliance at full dose and did experience a reduction in relapse rate on treatment despite the EDSS increase.

Before DMF treatment, 12 of 13 children (92%) had a baseline brain MRI scan performed. One child had a clinical history of two attacks disseminated in space and time and an initial MRI consistent with MS, but did not undergo repeat imaging immediately before starting DMF. Of the 12 children with pretreatment baseline MRI scans, six (50%) displayed new T2 lesions and four (33%) had gadolinium-enhancing lesions. Of the nine children treated with DMF for at least one year, three (33%) displayed new T2 lesions on brain MRI scans obtained after 12 months of therapy. One of these three children reported medication nonadherence.

Tolerability and side effects

Observed treatment-related side effects are summarized in Table 2. The most frequently reported side effects were facial flushing, occurring in eight children (62%), and