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Original Article

Safety and Efficacy of Delayed-Release Dimethyl Fumarate in Pediatric Patients With Relapsing Multiple Sclerosis (FOCUS)

Raed Alroughani [a], Rajiv Das [b], Natasha Penner [b], Joe Pultz [b], Catherine Taylor [b], Satish Eraly [b,*]

[a] *Dasman Diabetes Institute, Dasman, Kuwait and Amiri Hospital, Sharq, Kuwait*
[b] *Biogen, Cambridge, Massachusetts*

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ABSTRACT

Background: No therapies have been formally approved by the Food and Drug Administration for use in pediatric multiple sclerosis, a rare disease.
Objective: We evaluated the safety, efficacy, and pharmacokinetics of dimethyl fumarate in pediatric patients with multiple sclerosis.
Methods: FOCUS, a phase 2, multicenter study of patients aged 10 to 17 years with relapsing-remitting multiple sclerosis, comprised an eight-week baseline and 24-week treatment period; during treatment, patients received dimethyl fumarate (120 mg twice daily on days one to seven; 240 mg twice a day thereafter). Magnetic resonance imaging scans were obtained at week –8, day 0, week 16, and week 24. The primary end point was the change in T2 hyperintense lesion incidence from the baseline period to the final 8 weeks of treatment. Secondary end points were pharmacokinetic parameters and adverse event incidence.
Results: Twenty of 22 enrolled patients completed the study. There was a significant reduction in T2 hyperintense lesion incidence from baseline to the final eight weeks of treatment ($P = 0.009$). Adverse events (most commonly gastrointestinal events and flushing) and pharmacokinetic parameters were consistent with adult findings. No serious adverse events were considered dimethyl fumarate related.
Conclusions: Dimethyl fumarate treatment was associated with a reduction in magnetic resonance imaging activity in pediatric patients; pharmacokinetic and safety profiles were consistent with those in adults. Dimethyl fumarate is a potential treatment for pediatric multiple sclerosis.

Introduction

Pediatric multiple sclerosis (MS) is a rare disease. Although approximately 2% to 5% of all MS cases are estimated to have an onset before the age of 18 years,[1] the proportion of persons younger than 18 years old among patients with MS is expected to be substantially lower, because at any given point in time the great majority of patients with pediatric onset of disease would be adults. In fact, the worldwide pooled prevalence of pediatric MS in countries where data are available is 0.57 per 100,000, compared with 72.3 per 100,000 for adult MS.[2]

The degree to which adult and pediatric MS are pathophysiologically similar has been debated given age-related differences in the extent of inflammation and demyelination. Notably, pediatric MS almost invariably presents with a relapsing-remitting course characterized by a high relapse rate, rather than with a progressive course.[1,3-5] However, inflammation and demyelination are components of the disease regardless of age and are present even in patients in the later progressive phase.[5] Thus, the totality of evidence suggests that although quantitative differences may exist, adult and pediatric MS share the same basic disease mechanisms of inflammation, demyelination, and neurodegeneration.[5,6] Further support for this view would be provided by demonstration that therapies effective for adult MS also are effective for pediatric MS.

No disease-modifying therapies have yet been approved by the Food and Drug Administration or extensively studied in interventional, prospective clinical trials for use in pediatric patients with MS. The efficacy and safety of interferon beta (IFN-β) and glatiramer acetate, the most commonly used agents in pediatric MS, have been almost exclusively assessed in observational studies (the European Medicines agency has granted limited approval for the use of IFN-β in patients ≥12 years of age).[4,7,8] Most recently, the PARADIGMS study has published final results showing that children and adolescents with MS had an 82% lower relapse

Trial registration: ClinicalTrials.gov, NCT02410200. https://clinicaltrials.gov/ct2/show/NCT02410200.

* Corresponding author.
E-mail address: Satish.eraly@biogen.com (S. Eraly)

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rate with fingolimod versus IFN-β1a, but as yet fingolimod is not approved for the treatment of pediatric MS. Current recommendations regarding the use of these agents in pediatric patients, including dosing, are based on adaptation of adult treatment guidelines and expert opinion.

In adult patients with relapsing-remitting MS (RRMS), delayed-release dimethyl fumarate (DMF; also known as gastro-resistant DMF) has demonstrated strong efficacy and a favorable benefit-risk profile in two phase 3 studies (DEFINE and CONFIRM)[9,10] and an associated long-term extension study (ENDORSE).[11] Currently, there are few published data available on use of DMF to treat children or adolescents with MS.[12] The objective of FOCUS was to evaluate the efficacy, pharmacokinetics (PK), and safety of DMF in pediatric patients with MS.

Patients and Methods

Study design and participants

This study, entitled "Open-Label, multicenter, multiple-dose study of the effect of DMF on MRI Lesions and PK in pediatric subjects with RRMS aged 10 to 17 years" (FOCUS) was a phase 2, single-arm, multicenter, open-label study in pediatric patients with RRMS conducted between June 2015 and September 2016 at 12 sites across ten countries: Poland (n = 5), Kuwait (n = 3), Germany (n = 3), Bulgaria (n = 3), Turkey (n = 2), Lebanon (n = 2), Latvia (n = 1), Belgium (n = 1), Czech Republic (n = 1), and the United States (n = 1). The study comprised a four-week screening period, an eight-week off-treatment baseline period, and a 24-week treatment period (Fig 1). A safety follow-up visit was conducted four weeks after the last dose of study treatment.

During the eight-week baseline period, all patients were off MS treatment and underwent baseline brain magnetic resonance imaging (MRI) scans at week –8 and day 0. During the treatment period, clinic visits were conducted on day 1, day 8, and weeks 4, 8, 12, 16, and 24, with follow-up brain MRIs at weeks 16 and 24. Eligible patients had the opportunity to continue to receive DMF for up to an additional two years (extension study; ClinicalTrials.gov, NCT02555215; data not shown).

The study was conducted in accordance with relevant US federal regulations, the Declaration of Helsinki, and the International Council on Harmonisation Guideline for Good Clinical Practice. Approvals were granted by relevant institutional ethics committees for study protocol and amendments, and written assent and consent forms were obtained from each patient and his or her parent or legal guardian. FOCUS was registered at ClinicalTrials.gov (NCT02410200).

Eligible patients included males and females aged 10 to 17 years at the time of enrollment, with body weight ≥30 kg and a diagnosis of RRMS according to both the McDonald[13] and the International Pediatric Multiple Sclerosis Study Group criteria for pediatric MS.[14] Included patients also had to be ambulatory, with an Expanded Disability Status Scale score of ≤5.0, and had to have experienced at least one relapse in the 12 months or two relapses in the 24 months before screening.

The main exclusion criteria were progressive MS, disorders mimicking MS, or a history of clinically significant comorbid disorders or conditions. Patients were also excluded if they received prior medications such as DMF (at any time); fingolimod, teriflunomide, or natalizumab (within 6 months before week –8 MRI); or glatiramer acetate, IFN-β, or corticosteroids (within 28 days before week –8 MRI).

Procedures

During the 24-week open-label treatment period, all patients received DMF 120 mg twice a day (BID) for the first week (day one to day seven), and DMF 240 mg BID, the approved dosage for adult patients, thereafter.[15,16] DMF was temporarily or permanently discontinued if any laboratory values, including lymphocyte count, met predefined thresholds.[15] Assessments continued during the periods of treatment discontinuation, and resumption of treatment was considered on an individual basis depending on normalization of laboratory values. Compliance with study treatment dosing was monitored and recorded by study site staff.

Protocol-defined relapses (onset of new or recurrent neurologic symptoms not associated with fever or infection, of duration ≥24 hours, and accompanied by new objective neurologic findings) were treated at the discretion of the study investigator using the protocol-approved treatment for relapse (either three days or five days of intravenous methylprednisolone 1000 mg/d).

Outcomes

MRI scans were read by an independent central MRI center using advanced image analysis to limit variance. The eight-week interval between MRI scans at baseline and follow-up was chosen as the minimum period to allow a statistically reliable determination of incidence of new or newly enlarging T2 hyperintense lesions, con-

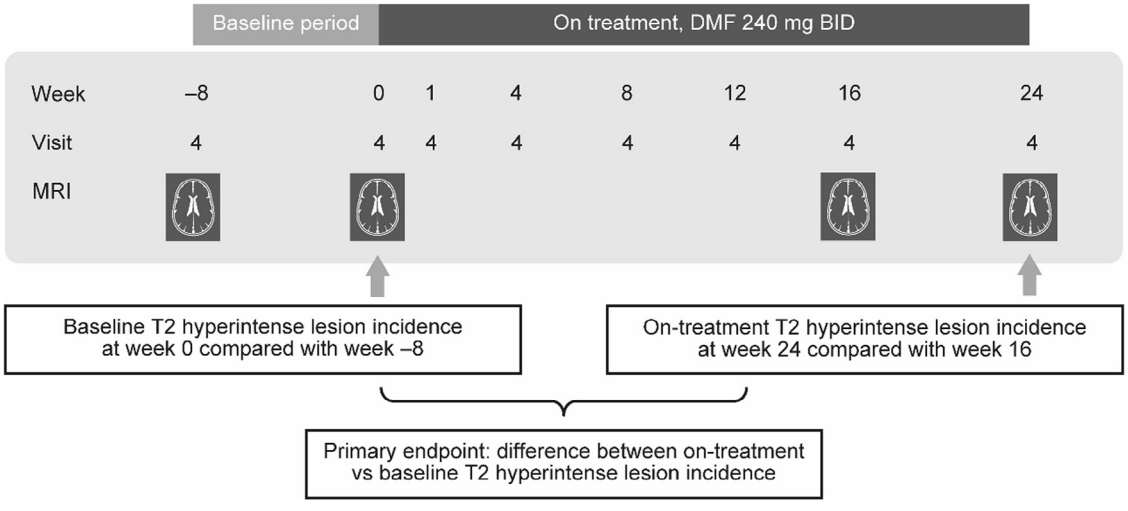

FIGURE 1. Design of the FOCUS study. BID, twice a day; DMF, delayed-release dimethyl fumarate; MRI, magnetic resonance imaging.