Neuronal and glial CSF biomarkers in patients with secondary progressive multiple sclerosis treated with dimethyl fumarate

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BACKGROUND

Delayed-release dimethyl fumarate (DMF, also known as gastro-resistant DMF) is approved for the treatment of patients with relapsing multiple sclerosis (MS). Evidence suggests that the pathogenesis of MS involves inflammation-driven oxidative injury in the central nervous system (CNS). Studies in rodents suggest that monomethyl fumarate (MMF), the primary and measurable metabolite of DMF, penetrates into the brain and cerebrospinal fluid (CSF). The CSF levels of MMF in humans after DMF treatment have not been evaluated. There is also no data on the effect of DMF treatment on neuronal and glial biomarkers.

Objectives: To investigate the pharmacokinetics of MMF in plasma and CSF in subjects with secondary progressive MS (SPMS), and to explore the effect of DMF on neuronal and glial biomarkers.

METHODS

Sixteen SPMS patients with no prior DMF exposure were treated with oral DMF 120 mg twice daily (BID) for 4 weeks, followed by DMF 240 mg BID for 24 weeks. During Week 6 (the second week on DMF 240 mg), plasma samples were collected before the morning dose and then at 2, 3, 5, 6, 7, 8 and 10 hours post morning dose. On the day of PK sampling, the patients took a morning dose after a low fat meal at the clinic. CSF samples were collected at pre-dose or 3, 5, 7 or 10 hours post-dose (3-4 patients at each time point). Baseline demographics are described in Table 1. MMF concentrations in plasma and CSF samples were determined by liquid chromatography-mass spectrometry (LC-MS). CSF levels of neurofilament light (NfL), tau, glial fibrillary acidic protein (GFAP) and ubiquitin carboxyl-terminal hydrolase isozyme L1 (UCH-L1) were measured at baseline, week 6 and week 28.

Table 1. Patient demographics (baseline and end of study)

SPMS Patients	n = 16	Range
Female, %	87.5	n/a
Caucasian, %	100	n/a
Age, years	55.4 (8.93)	37 - 65
EDSS: Baseline	4.44 (1.56)	3 – 6.5
EDSS: End of study *n = 13	3.31 (1.56)*	1.5 – 6.5*
Disease duration, years	22.5 (11.7)	3 – 39
MS Relapses in past 12 months	0.19 (0.40)	0 – 1
Gad+ lesions at baseline	0 (0)	0

Data are mean (SD), n(%), unless otherwise stated. MS = multiple sclerosis. EDSS= expanded disability status scale.

RESULTS: PK

Figure 1. Mean (± SE) MMF Plasma and CSF Concentrations after 240 mg BID doses of DMF

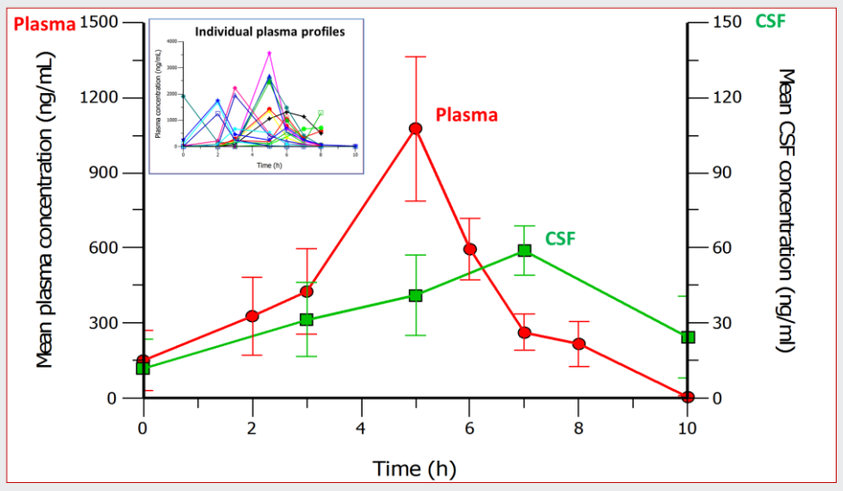


Table 2: Pharmacokinetic Parameters of MMF in Plasma and CSF

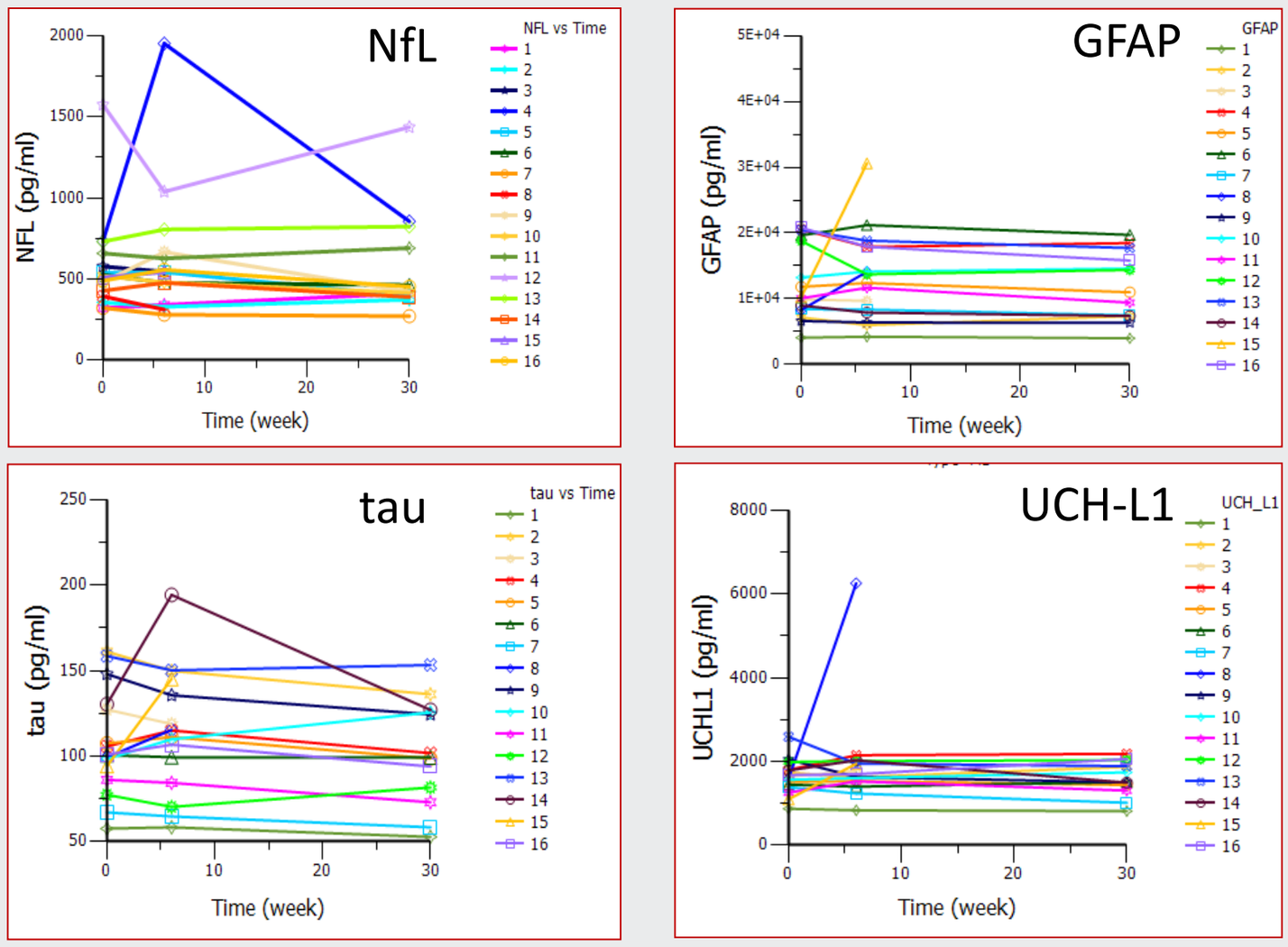
Parameter	Plasma	CSF	CSF/Plasma ratio
AUC_{inf}, h*ng/ml	4090	455	**11%**
T_{max}, h	5	7	

MMF readily penetrates into CNS as measured by its CSF levels

AUC = area under the curve

Biomarkers

Figure 2. NfL, total tau, GFAP and UCHL1 levels in CSF of SPMS patients over the course of 30 weeks treatment with DMF



- After oral administration, DMF is rapidly converted to its active metabolite MMF, and DMF is not quantifiable in plasma. In this study, the highest CSF level of MMF was at 7 hours post-dose, lagging behind plasma T_{max}, with maximal CSF concentration of 39–79 ng/mL (Figure 1).
- The mean CSF-to-plasma exposure ratio for MMF is 11% (Table 2).
- Mean EDSS decreased to 3.3, reflecting clinical improvement in 9 of 13 patients (Table 1).
- Tau, GFAP and UCH-L1 levels remained stable over the course of treatment.
- Baseline CSF NfL levels in SPMS patients were 572±296 pg/mL. NfL remained stable over the course of DMF treatment to week 28 (569±316 pg/mL), except for an increase in one patient with disease exacerbation at week 18.

CONCLUSIONS

- MMF readily penetrates into the CNS as measured by CSF levels
- CSF NfL was stable except for an increase in one patient upon disease exacerbation, consistent with the proposed value of NfL as a marker of MS disease activity and treatment monitoring

Disclosures:
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BZ, TP, JPM, NP: employees of and holds stock/stock options in Biogen
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