A pilot study to assess disease state stability, efficacy, and tolerability in a natalizumab to dimethyl fumarate crossover design

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BACKGROUND:
While natalizumab therapy is highly efficacious for the treatment of multiple sclerosis (MS), it does carry significant risk for progressive multifocal leukoencephalopathy (PML) in patients who have an immunosuppressant history. >24 natalizumab doses, and JCV index of >1.5. A crossover to dimethyl fumarate (DMF) has not been previously studied. A previous exploratory study involving natalizumab discontinuation (RESTORE) found a 15-29% relapse rate and a 7-53% MRI activity (disease recurrence) rate during the 24 week observational period. (Neurology, 2014 Apr 29;82(17):1491-8)

OBJECTIVES:
To determine disease stability for 24 weeks in patients who have crossed over from natalizumab to DMF.

METHODS:
Thirty subjects at high risk (>2 years on therapy, JCV index >1.5) for developing PML on natalizumab and scheduled for crossover to DMF were enrolled in an observational exploratory trial to monitor the transition. At baseline, most patients were dose interval extended with a mean interval in the prior six cycles of 34.6 days per standard clinic risk mitigation protocol. Disease stability at baseline was assessed with minimal relapses seen in the prior six months and no new or gadolinium enhancing lesions seen at baseline. A single patient had a single enlarging T2 lesion. Patients received DMF 120 mg BID, three weeks post last dose of natalizumab for one week, then DMF 240 BID. Patients were observed for 24 weeks starting at onset of last dose of natalizumab. Outcome measures included proportion of patients with natalizumab reversion, clinical relapse and significant MR change. Quality of life metrics (Visual Analogue Scale, VAS) Modified Fatigue Impact Scale (MFIS) cognition (Symbol Digit Modality Test, SDMT), Expanded Disease Status Scale, and 25 ft timed walk were also collected and will be reported separately. Brain MRI with spectroscopy was obtained at 0, 4, 12, 24 weeks (P<0.454). An additional post study observation period of 24 weeks is also planned for all subjects.

RESULTS:
Thirty patients initially enrolled. A single patient reverted to natalizumab for nonmedical reasons leaving 29 patients for analysis. No tolerability

CONCLUSIONS:
Approximately three-fourths of patients were able to successfully transition from natalizumab to DMF. Most relapses and MRI disease activity occurred at 16 weeks or later although a number of relapses were seen prior to that point. No reversions due to adverse events associated with DMF were identified.

No evidence for natalizumab cessation induced “rebound” was identified in any patient. Minimal disease activity by relapse and MR criteria was seen on steady state natalizumab therapy with an extended mean infusion cycle length at baseline.

DMF appears to be a viable post natalizumab option for the majority of patients at higher risk for PML. Further study is warranted.