The results of a controlled, prospective study of relapsing MS patients at risk for PML who switched from long term natalizumab to teriflunomide in a controlled, prospective study.

K. Edwards[1] , S.Cohan[2], J. O'Connor[1] , J. Siuta[1], J. Thomas[3], C. Chen[2], T. Gervasi[2], K. Smoot[2], & K. Kresa-Reahl[2]

[1] MS Center of Northeastern New York (Latham, NY, USA); [2] Providence Multiple Sclerosis Center (Portland, OR, USA)
[3] Community Care Physicians P.C. (Latham, NY, USA)

BACKGROUND

Natalizumab (NTZ) has the risk of causing progressive multifocal leukoencephalopathy (PML) in patients after extended use and with detectable anti-JCV-antibodies. There is a need for alternative disease modifying treatment (DMT) that would be safe and effective to prevent recurrence of MS exacerbations upon discontinuation of NTZ without further risk of PML. Platform DMTs have been ineffective in preventing rebound of MS activity. Fingolimod and dimethyl-fumarate (DMF) have associated with PML. No cases of PML have been associated with teriflunomide in 70,000 patients.

OBJECTIVES

To explore the safety and efficacy of teriflunomide in patients switching from NTZ to teriflunomide in MS patients at risk for PML.

METHODS

Patients with relapsing multiple sclerosis (RMS) must have received 12 or more NTZ treatments and be anti-JCV-ab positive and not have had prior immunosuppressive therapy. Patients had to be free of clinical relapses during prior 12 months of NTZ treatment. RMS patients ages 21 to 65 began teriflunomide at 14mg daily, within 4 weeks after last dose of NTZ. Relapse assessment, EDSS, 3T brain MRI, laboratory tests were performed at baseline and monthly for 6 months. Final assessments were done at 12 months.

RESULTS

There were 58 patients screened and 51 enrolled. Mean age was 47 (SD 10.16). Seventy-four percent were female. The mean EDSS at baseline was 3.03 (SD 1.35); 45 patients completed 12 months with mean EDSS of 2.98 (SD 1.44). The mean number of NTZ treatments prior to treatment with teriflunomide was 41 (SD 25.64)
MRI results showed 36 patients (71%) stable in all parameters from baseline to month 12. There were 15 patients with new MRI activity during the first 12 months, of which 14 had Gd+ enhancing lesions, mostly 3-5 mm and transient. One with minor Sx resolved with IVMP. Most of the patients with new MRI lesions had no symptoms. Only three patients required change of DMT due to MRI progression. Three patients dropped out of the study due to adverse events or lack of efficacy.

Table 1: Patient demographics and clinical data

Patients switched from natalizumab to teriflunomide, n=51	Percentage	Mean (SD)	Range
Female (n=38)	74%	n/a	n/a
Age (n=51)	n/a	47.76 (10.28)	26-62
Total No of years of MS	n/a	15.27 (7.83)	3.78-39.78
Baseline EDSS	n/a	3.03 (1.35)	1.0 - 6.0
EDSS at month 12	n/a	2.98 (1.44)	1.0 – 6.0
Number of natalizumab infusions (SD)	n/a	41 (25.64)	12 - 114
Mean # of prior DMTs before NTZ (SD)	n/a	2.71 (1.01)	n/a

CONCLUSIONS

These results show that, in the majority of patients, teriflunomide may be a rational choice for long term safety and efficacy for patients at risk for PML. Early switch, in fewer than 4 weeks, from NTZ to teriflunomide, may be important to suppress ongoing ´rebound´ and recurrent MS activity after stopping NTZ.

REFERENCES

1. Petty M et. al *Neurology* 2010;74:Suppl2:A415. abstract
2. Miravelle A et al *Arch Neurol* 2011; 68:186-91
3. Havla J et al. P536. *Multiple Sclerosis Journal* 2012; 18: (S4) 230
4. O' Connor P et al. N Engl J Med 2011;365:1293-303.
5. Confavreux C et al. Lancet Neurol 2014;13:247-56

Table 2: Data at Month 12

#	Patient #	Age	Gender	EDSS at Baseline	EDSS at Month 12	EDSS Status	# of Exacerbations 1 year prior to NAT start	# of GAD Enhancing Lesions on MRI 1 year prior to NAT start	# of New Gd+ on MRI	# of New or enlarging T2 on MRI	Lesions occurring at Month #	MRI Activity	Clinical Relapse
1	101	44	Female	3	4	Worse by 1.0	2	0	0	1	Month 12	Yes	No
2	102	42	Female	3.5	2	Improved by 1.5	2	0	0	0	-	-	No
3	103	42	Male	2	2	No change	2	1	3	5	Month 6,12	Yes	No
4	104	57	Female	6	6	No change	3	0	0	0	-	-	No
5	105	40	Female	4.5	6	Worse by 1.5	1	0	0	0	-	-	No
6	106	42	Female	3	2.5	Improved by 0.5	2	3	0	0	-	-	No
7	107	54	Female	6	6.5	Worse by 0.5	2	4	0	0	-	-	No
8	108	43	Female	3.5	1.5	Improved by 2.0	3	0	2	1	Months 3 and 4	Yes	No
9	109	49	Female	2	1.5	Improved by 0.5	1	0	0	0	-	-	No
10	110	57	Male	2	2	No change	4	0	0	0	-	-	No
11	111	52	Female	4	4	No change	5	1	0	1	Month 12	Yes	No
12	113	57	Female	4	5.5	Worse by 1.5	0	0	0	0	-	-	No
13	114	40	Female	2.5	2.5	No change	2	1	0	0	-	-	No
14	115	48	Female	3	3	No change	2	0	2	6	Month 12	Yes	No
15	117	51	Female	2.5	2	Improved by 0.5	0	0	0	2	Month 12	Yes	No
16	118	59	Female	3.5	3.5	No change	0	0	0	0	-	-	No
17	119	58	Male	4	4	No change	1	0	0	1	Month 6	Yes	No
18	120	40	Female	2.5	1	Improved by 1.5	3	1	0	0	-	-	No
19	121	42	Female	4	3.5	Improved by 0.5	2	0	0	0	-	-	No
20	122	37	Male	1	1	No change	2	1	0	2	Month 5,12	Yes	Yes
21	123	54	Female	4	2.5	Improved by 1.5	2	8	0	0	-	-	No
22	124	31	Male	4	3	Improved by 1.0	2	0	0	0	-	-	No
23	126	62	Male	1	2	Worse by 1.0	2	0	0	0	-	-	No
24	127	20	Female	3	ET at Month 4	ET	1	30	12	0	Month 4	Yes	ET due to MRI progression at Month 4
25	128	57	Male	2.5	4	Worse by 1.5	1	1	0	0	-	-	No
26	130	36	Female	3.5	3.5	No change	1	0	1	1	Month 12	Yes	No
27	131	46	Female	1.5	2.5	Worse by 1.0	0	6	0	0	-	-	No
28	132	47	Male	1.5	2	Worse by 0.5	3	0	0	0	-	-	No
29	133	59	Female	2	2.5	Worse by 0.5	1	0	0	0	-	-	No
30	134	39	Male	1.5	1.5	No change	1	1	0	0	-	-	No
31	135	44	Female	3.5	5.5	Worse by 2.0	2	0	0	0	-	-	No
32	136	50	Female	2	3.5	Worse by 1.5	1	0	0	0	-	-	No
33	137	51	Female	2.5	2	Improved by 0.5	2	0	0	0	-	-	No
34	138	33	Female	2.5	2.5	No change	0	2	0	0	-	-	No
35	139	64	Female	5.5	5.5 at Mo 4	No change	1	0	0	0	-	-	ET at Month 4 due to GI side effects
36	201	41	Female	2	2	No change	2	0	0	0	-	-	No
37	204	26	Female	2.5	2.5	No change	1	0	1	0	Month 6,12	Yes	Yes
38	205	52	Male	2.5	2	Improved by 0.5	1	0	0	0	-	-	No
39	206	31	Male	2	*		7	10	5	3	Months 3 and 5	Yes	Yes DCD teriflunomide at month 6 due to MRI progression
40	207	49	Female	2	2.5	Worse by 0.5	0	0	0	0	-	-	No
41	208	45	Female	5	4.5	Improved by 0.5	0	0	0	0	-	-	No
42	209	58	Female	6	6	No change	0	0	0	0	-	-	No
43	210	57	Female	1.5	2	Worse by 0.5	1	1	0	1	Month 2	Yes	No
44	211	60	Female	2	2	No change	0	0	0	0	-	-	No
45	212	56	Female	3	3	No change	0	0	0	0	-	-	No
46	213	58	Male	2	1.5	Improved by 0.5	1	0	1	1	Month 6	Yes	No
47	214	50	Female	3.5	3.5	No change	0	0	0	0	-	-	No
48	215	63	Female	5	4.5	Improved by 0.5	1	0	0	0	-	-	No
49	216	35	Female	2	2	No change	1	0	10	5	Months 3,4,6	Yes	Yes DCD teriflunomide at month 4 due to MRI progression
50	218	47	Female	1.5	1.5	No change	1	0	0	0	-	-	No
51	219	63	Male	1.5	2	Worse by 0.5	0	0	0	0	-	-	No

Disclosures:
KE received research support from Biogen, Genentech, Genzyme/Sanofi, Eli Lilly, Novartis; SC serves on steering committees and advisory boards for Biogen, Novartis, Sanofi-Genzyme and Mallinckrodt, receives research support from Biogen, Novartis, Sanofi-Genzyme, Roche, Opexa, Mallinckrodt and Genentech, receives speaking honoraria from Biogen, Novartis, Sanofi-Genzyme and Acorda; KS received research support from Biogen and consulting fees from Acorda, Biogen, EMDSerono, Genzyme, Novartis, and Teva; KKR received speaking honoraria from Biogen, Novartis, TEVA, Mallinckrodt, and Genzyme and grant support from Biogen, Novartis, Mallinckrodt, and Genzyme and consulting fees from EMDSerono and Genentech, JO, JS, JT, CC, TG have nothing to disclose.

Supported by an unrestricted educational grant from Genzyme/Sanofi
Presented at the 7th Joint ECTRIMS-ACTRIMS Meeting, 25-28 October 2017, Paris, France