Brain Atrophy Analysis of Relapsing-Remitting Multiple Sclerosis Patients Treated with Pioglitazone

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Introduction

Pioglitazone is an FDA-approved agonist of the peroxisome proliferator-activated receptor gamma (PPARg). It has shown to reduce clinical and histological symptoms in the demyelinating disease experimental autoimmune encephalomyelitis (EAE) in animals; and a case report has suggested efficacy in secondary progressive multiple sclerosis (SPMS) [1]. We carried out a placebo-controlled phase-I clinical trial of Pioglitazone (30 mg daily, p.o.) in relapsing-remitting MS (RRMS) patients with mild to moderate EDSS scores and taking Avonex to monitor longitudinal changes in the characteristics of brain atrophy and lesion burden.

Methods

Twenty two RRMS patients (mean age=43 +/- 5 years) were recruited for the study. MRI scans were performed on a 3T whole-body MR system (EXCITE 2.0 Signa GE Healthcare, Milwaukee, USA) at University of Illinois, Chicago. Three dimensional Fast Spoiled Gradient Recalled (FSPGR) images of the whole brain were acquired in the axial plane with the gradient echo technique. Fast fluid attenuated inversion recovery (FLAIR) data were acquired with two repetitions. Follow-up MRI scan was carried out at 12 months after the baseline. The research protocol was approved by the local Institutional Review Board and informed written consents were obtained from all patients.

SPGR images were segmented for the quantification of gray matter, white matter, and brain parenchyma volumes. The tissue segmentation was performed using the Matlab program written by Christian Gaser [2] built in statistical parametric mapping (SPM2) software [3]. Wilcoxon Signed Ranks test for two related samples was used to model changes in SPGR derived parameters over time.

FLAIR images were analyzed by semi-automated approach for the estimation of lesion burden using Medx (Medical Numerics, Inc., Sterling, VA) software. Follow up image was coregistered with the baseline image and seed voxel was selected at the center of all conspicuous lesions. The software automatically finds all voxels with the same intensity as the seed voxel based on least square distance method. A neurologist confirmed the results and made modifications to reduce artifacts. The volume for the segmented lesions was then calculated. Between groups (placebo and treatment) comparison was done by two sample t-test assuming equal variances. Relationships between changes in brain atrophy and lesion burden were obtained by correlation analysis using Pearsons' method.

Results

The ratios of brain measure means (± SD) and Wilcoxon Signed Ranks test results for treatment and placebo groups are presented in Table 1. Ratio is obtained as one year from baseline divided by baseline values. A significant reduction in gray matter volume loss of the treatment group occurred compared to the placebo group (p=0.03, Wilcoxon Signed Ranks test), and there was a trend towards a reduced loss of overall brain parenchyma in the treatment group compared to the placebo group (p=0.09). Gray matter atrophy over 1 year was inversely correlated to patient age in the placebo group, but not in the treatment group.

Table 1: Summary of brain volume measure mean results using Wilcoxon singed ranks test

Brain Measure Ratio (time 3: time 1)	Placebo Group (n=10) Mean ± SD	Treatment Group (n=11) Mean ± SD	Difference Mean ± SD (*p*)
Gray Matter Volume	5.8 ± 2.0 % loss	3.1 ± 3 % loss	- 2.7 ± 0.3 % (*p*=0.03)
White Matter Volume	3.3 ± 1.8 % loss	3.8 ± 2.7 % loss	+ 0.6 ± 0.9% (*p*=0.09)
Brain Parenchyma	4.8 ± 2.1 % loss	3.4 ± 2.3 % loss	- 1.4 ± 0.2 % (*p*=0.09)

After 1 year, the total FLAIR lesion volume increased 3% in the placebo group; but was reduced 6% in the treatment group, and this difference was significantly different (P < .05 unpaired T-test assuming equal variances). In the placebo group, the increase in FLAIR lesion volume was positively correlated with the increase in T1 lesion volume which occurred over 1 year; this correlation was absent in the treatment group. The relationship between changes in gray matter atrophy and FLAIR and T1 lesion volumes will be presented.

Discussion and Conclusion

The significant difference in gray matter volume between treatment and placebo groups is in agreement with previous studies [4,5] and provides the pathologic evidence of gray matter involvement in RRMS. These results suggest that gray matter atrophy can be used as a surrogate marker to monitor disease course and assess the impact of therapeutic interventions. The inverse correlation of gray matter atrophy with age in the placebo group is consistent with the idea that pathological changes occur early in the disease process, and suggests that treatment may selectively influence early events. Prospective studies to determine the biological factors associated with atrophy progression, it's correlation with cognitive impairment and radial and axial diffusivities are underway. The effect of drug treatment on FLAIR lesion burden further supports a beneficial effect of Pioglitazone in patients with RRMS. Further testing of this drug in larger cohort of MS patients is therefore warranted.

References:

1. Feinstein, D.L. et. al., Biochem Pharmacol: 70,177 (2005); 2. Christian Gaser (http://dbm.neuro.uni-jena.de/vbm.htm); 3. Statistical Parametric Mapping (version SPM2) (Wellcome Department of Cognitive Neurology, London, UK); 4. C. Oreja-Guevara et. Al.: 62, 578 (2005); 5. Tiberio, M. *et. al.*, Neurology, 64: 1001 (2005).