Towards Assessing White Matter Integrity in Patients with Relapsing-Remitting Multiple Sclerosis 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). 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 intrinsic brain tissue properties.

Methods

Twenty two RRMS patients were recruited for the study; 11 placebo, 11 Pioglitazone (mean age=43 +/- 5 years). MRI scans were performed on a 3T whole-body MR system (EXCITE 2.0 Signa GE Healthcare, Milwaukee, USA) at University of Illinois, Chicago. Diffusion tensor imaging (DTI) data were acquired using single shot echo-planar imaging (EPI) pulse sequence with two degrees of diffusion weighting (b = 0 and 750 s/mm^2). DTI data were acquired in 26 non-linear directions 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.

Region-of-interest (ROI) based analysis of DTI data was carried out to estimate DTI parameters (relative anisotropy (RA), apparent diffusion coefficient (ADC), axial and radial diffusion for corpus callosum. ROIs were drawn manually to segment these anatomical regions on B0 images using Analyze software (Mayo Clinic, Rochester, MN). Six representative slices were selected so that ROIs will cover body, genu, and splenium of corpus callosum. These segmented ROIs were saved as individual objects and then applied to DTI maps in order to calculate the mean values for each object.

Furthermore, in order to study the predictive usefulness of DTI method in a clinical trial settings, we defined ROIs based on following criteria: (1) regions which appeared normal at the baseline and also appeared normal after one year, (2) regions which appeared normal at baseline but converted into lesion after one year, and (3) regions which appeared lesion at the baseline and also after one year with apparent changes in disease activities in surrounding tissue. Conspicuity of lesion and appearance were determined from FLAIR images obtained at baseline and after one year. Between groups (placebo and treatment) comparison was done by Wilcoxon Signed Rank test.

Results

When we compared the changes in placebo and Pioglitazone groups for corpus callosum, significant difference in ADC and radial diffusion between the two groups was observed. ADC was increased 3.1 ± 0.03% in placebo and 5.7 ± 0.03% increase in Pioglitazone group (p = 0.05). Increase in radial diffusion was 4.2 ± 0.05% in placebo and 10.9 ± 0.07% in Pioglitazone group (p = 0.04). A non significant (p = 0.62) increase in axial diffusion (2.4 ± 0.02% in placebo and 1.9 ± 0.02% in Pioglitazone) and non significant loss of RA (1.3 ± 0.08% in placebo and 5.9 ± 0.06% in Pioglitazone) was also found.

Regions which appeared normal at the baseline but converted into lesions after one year had lower RA (0.18 versus 0.19), higher ADC (0.80 versus 0.78), and higher radial diffusion (1.07 versus 1.04) as compared to those regions which appeared normal at the baseline and also appeared normal after one year. Interestingly, the axial diffusivity was also higher (0.67 versus 0.64) at the baseline. These results did not reach statistical significance (p>0.05) still they suggest the sensitivity of DTI measurements in RRMS.

In the placebo group, ROIs which at baseline showed both high ADC and high axial diffusion had a >80% chance to develop into lesions, while similar ROIs in the Piogliazone group had a <10% chance to develop into lesions (Figure 1).

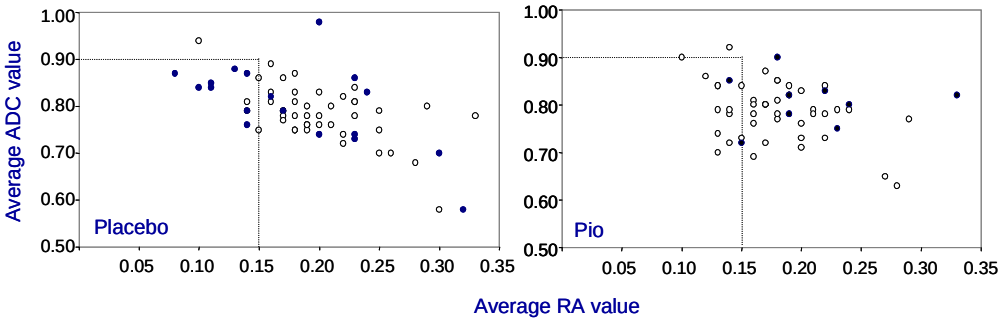

Figure1: Plot of baseline values for average RA versus average ADC for NAWM >> Lesion and NAWM >> NAWM ROIs that were located across FLAIR images.

Discussion and Conclusion

These results suggest that DTI parameters are sensitive markers to study the disease progression and may have the potential to be predictive of pathological changes in RRMS. Pioglitazone may improve anisotropy and reduce mean diffusivity at the site of degenerating tissue in RRMS patients. Further testing of this drug in larger cohort of MS patients is therefore warranted.