June 2022

The Effect of Disease Modifying Therapies on Deep Gray Matter: A Longitudinal Comparative Study

Wendy Jin
hf2832@wayne.edu

Evanthia Bernitsas
Wayne State School of Medicine

The Effect of Disease Modifying Therapies on Deep Gray Matter: A Longitudinal Comparative Study

Wendy, Jin, Evanthia Bernitsas, MD, FAAN

Summary

Cerebral gray matter (GM) atrophy is an important factor in determining disability in Multiple Sclerosis[4,9]. Disease modifying therapies reduce the GM atrophy to some degree, both in the cortical and deep gray matter (dGM). A previous study has shown that fingolimod (FTY720), asphingosine 1 phosphate immunomodulator can significantly reduced GM and thalamic volume loss in patients with relapsing-remitting Multiple Sclerosis(RRMS)[1]. In addition to its effect on reducing dGM volume loss, fingolimod is also believed to have protective effect on focal and diffuse dGM damage[2,8]. The effect of natalizumab on GM atrophy, however, is controversial[5]. Although compared with fingolimod, natalizumab- treated patients had a smaller number of areas of cortical GM atrophy, particularly in temporo-occipital regions, natalizumab-treated patients experienced accelerated GM atrophy in cerebellum. The effect of natalizumab on dGM atrophy is still unclear. glatirameracetate, another disease modifying agent, has shown a reduction of the accumulation of cortical lesions and slowing of the GM atrophy progression[3].

Although the effectiveness offingolimod, glatiramer acetate and natalizumab on maintaining GM volume has been studied separately, data about comparative longitudinal effect of these therapies are limited[7, 10].Using clinical and MRI data on a 3T MRI that were collected over at least three years, we aim to provide acomprehensivecomparison of the effectofflingolimod, glatiramer acetate and natalizumab on the dGM.

The primary hypothesis of the study is that all three disease modifying therapies, fingolimod, glatirameracetate and natalizumab will reduce the dGM atrophy to a certain degree in RRMS patients over the study period. The secondary hypothesis is that fingolimod-treated patientsmay show less dGM volume loss compared with glatirameracetate and natalizumab-treated MS patients.

Methods

All participants, including patients starting on fingolimod (n=55), onnatalizumab (n=28) or glatiramer acetate (n=30) underwent MRI scans at baseline (Y0), one year after the initiation of the drug (Y1), two years after the initiation of the drug (Y2) and three years after the initiation of the drug (Y3). Changes in dGM volume, including thalamus, caudate, putamen, pallidum, hippocampus, amygdala, accumbens, and brain stem, were recorded. Changes in dGM were then analyzed from the following three perspectives.

- Correlations between Clinical Measures and dGM Volume

The dGMvolumeof all three drug-groups at Y0 was compiled. The correlation between patients' eight dGMstructures with their Y0 clinical data, including age, Expanded Disability Status Scale (EDSS), Disease Duration (DD), Functional Systems Scores(FSS), number of relapses, Timed 25-Foot Walk (T25W), 9-Hole Peg Test (9HPTD and 9HPTND), Paced Auditory Serial Additiona Test (PASAT-3), and Symbol Digit Modalities Test (SDMT) were analyzed.

- Comparison of Longitudinal Changes in dGM Volumewithin Each Drug Group

The changes in dGM volume between two time points, for example, Y0 and Y1 were analyzed using Wilcoxon Sighed Ranks test. Repeated Measures ANOVA test was used to compare three time points, for example, Y0, Y1, and Y2. For drug groups that have data from all three years, for example, fingolimod and natalizumab, both p value of the Test of Within-Subjects and p value of Pairwise Comparisons were recorded. Glatiramer acetate has data from Y0 and Y1, a Wilcoxon signed-rank test was done and p-value was recorded.

- Comparison of Different Drug effect on dGM Volume

The volume change in each dGM structure from two time points, i.e. Y0 to Y1, Y1 to Y2, Y2 to Y3, Y0 to Y2 and Y0 to Y3 in each drug group were calculated. One Way ANOVA test was run to compare the volume changes over the same time period within three drug-groups.

Results

EDSS is negatively correlated with the volume of thalamus ($p<0.001$), caudate ($p=0.048$), putamen ($p=0.026$), and accumbens ($p=0.015$). DD is negatively correlated with the volume of thalamus ($p=0.012$), caudate ($p=0.028$), putamen ($p=0.030$) and hippocampus ($p=0.026$). FSS is negatively correlated with the volume of thalamus ($p=0.015$). T25FW is negatively correlated with the volume of thalamus ($p<0.001$), caudate ($p=0.003$), putamen ($p<0.001$), pallidum ($p<0.007$), accumbens ($p=0.006$) and brain stem ($p=0.006$). 9HPT D is negatively correlated with the volume of thalamus ($p=0.014$) and the volume of pallidum ($p=0.023$). 9HPT ND is negatively correlated with the volume of thalamus ($p=0.019$), putamen ($p=0.02$) and pallidum($p=0.005$). PASAT is positively correlated with the volume of thalamus ($p=0.013$), caudate ($p=0.009$) and pallidum ($p=0.009$) but negatively correlated with the volume of putamen ($p=0.038$)(Table 1).

Patients onfingolimod showed significant decrease in the volume of pallidum from Y0 to Y1 ($p=0.008$) and Y0 to Y2 ($p=0.043$), and thalamic volume from Y0 to Y2 ($p=0.005$). Patients who tooknatalizumab showed significant decrease in volume of thalamus from Y0 to Y1 ($p=0.032$) (Table 2).

Over the same time period, patients from different drug groups did not show significant difference in the change in dGMvolume.

Conclusion

Patients who have smaller thalamus, putamen, caudate and accumbens tend to score higher EDSS score, indicating that the above structures are associated with more severe neurological impairment in MS. Patients who have lower thalamus, caudate, putamen, pallidum, accumbens and brain stem volume take longer to complete T25FW test, which shows deteriorated walking ability. Similar trend can be found in the upper extremity function in MS patients. Those with lower thalamic, putamen and pallidum volume perform worse in the 9HPT test. Higher cognitive function is correlated with higher thalamic, caudate, putamen and pallidum volume. Lastly, lowerthalamic, caudate, putamen and hippocampal volume is related to longer disease duration.

The majority of the patients in the study did not show significant reduction in dGM volume, which proves that all three disease modifying agents slowed down the dGM atrophy over the course of 3 years.Compared to natalizumab and copaxone, fingolimod patients showed more significant loss in the volume of pallidum.

Table 1.dGM and Clinical Measures

	Thalamus	Caudate	Putamen	Pallidum	Hippocampus	Amygdala	Accumbens	Brain Stem
Age								
r value	-0.034	-0.087	-0.087	0.077	-0.018	0.085	0.089	0.028
pvalue	0.727	0.372	0.372	0.430	0.853	0.382	0.362	0.774
EDSS								
r value	-0.362**	-0.196*	-0.221*	-0.134	-0.085	0.016	-0.240*	-0.104
pvalue	<0.001	0.048	0.026	0.178	0.394	0.874	0.015	0.297
DD								
r value	-0.243*	-0.214*	-0.212*	-0.171	-0.218*	-0.046	0.027	0.035
pvalue	0.012	0.028	0.030	0.082	0.026	0.638	0.784	0.726
FSS								
r value	-0.343*	-0.267	-0.225	-0.232	-0.035	-0.186	-0.188	-0.234
pvalue	0.015	0.061	0.117	0.106	0.811	0.196	0.192	0.102
# of relapses								
r value	0.075	0.205	0.234	0.237	0.193	-0.040	-0.062	-0.026
pvalue	0.721	0.325	0.260	0.255	0.354	0.850	0.770	0.902
T25FW								
r value	-0.445**	-0.332**	-0.411**	-0.302**	-0.177	-0.216	-0.309**	-0.305**
pvalue	<0.001	0.003	<0.001	0.007	0.119	0.056	0.006	0.006
9 HPT D								
r value	-0.460*	-0.330	-0.350	-0.429*	-0.163	-0.077	-0.190	-0.117
pvalue	0.014	0.086	0.068	0.023	0.408	0.696	0.332	0.554
9HPT ND								
r value	-0.442*	-0.344	-0.438*	-0.519*	-0.194	-0.201	-0.039	-0.169
pvalue	0.019	0.073	0.020	0.005	0.322	0.304	0.843	0.505
PASAT								
r value	0.478*	0.502**	-0.409*	0.503**	0.093	0.285	0.219	0.154
pvalue	0.013	0.009	0.038	0.009	0.650	0.157	0.282	0.453
SDMT								
r value	0.348	0.343	0.335	0.324	0.284	0.103	0.227	0.069
pvalue	0.065	0.069	0.075	0.086	0.136	0.594	0.237	0.732

**indicates significant linear relationship*

***indicates strong linear relationship*

Table 2. Longitudinal Comparison

	Thalamus	Caudate	Putamen	Pallidum	Hippocampus	Amygdala	Accumbens	Brain Stem
Fingolimod n=44 Repeated ANOVA								
P value Test of Within-Subject[†]	p>0.05	p>0.05	p>0.05	P<0.05*	p>0.05	p>0.05	p>0.05	p>0.05
P value Pairwise Comparisons[††]	Y0vs Y2* (p=0.005)	/	/	Y0 vs Y1* (p=0.008) Y0 vs Y2* (p=0.043)	/	/	/	/
Glatiramer acetate **n=20 Wilcoxon-signed Ranks**								
P value Y0 vs. Y1	0.970	0.455	0.084	0.370	0.550	0.179	0.514	0.654
Natalizumab n=16 Repeated ANOVA								
P value Test of Within-Subjects	P<0.05*	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05
P value Pairwise comparisons	Y0 vs Y1* (p=0.032)	/	/	/	/	/	/	/

**indicates significant p value*

[†]p-value, Test of Within-Subjects is the p value from ANOVA test among 3 time pints (Y0, Y1, Y2) for each measurement.

[††]p-value, Pairwise Comparisons is the p value from comparing two time points, as long as p value from ANOVA shows significance.

- References

1. *Gaetano L, Häring DA, Radue EW, et al. Fingolimod effect on gray matter, thalamus, and white matter in patients with multiple sclerosis. Neurology. 2018;90(15):e1324-e1332. doi:10.1212/WNL.0000000000005292*

2. Bajrami A, Pitteri M, Castellaro M, et al. The effect of fingolimod on focal and diffuse grey matter damage in active MS patients. J Neurol. 2018;265(9):2154-2161. doi:10.1007/s00415-018-8952-2

3. Crescenzo F, Marastoni D, Zuco C, et al. Effect of glatiramer acetate on cerebral grey matter pathology in patients with relapsing-remitting multiple sclerosis. MultSclerRelatDisord. 2019;27:305-311. doi:10.1016/j.msard.2018.11.009

4. Koskimäki F, Bernard J, Yong J, et al. Gray matter atrophy in multiple sclerosis despite clinical and lesion stability during natalizumab treatment. PLoS One. 2018;13(12):e0209326. Published 2018 Dec 21. doi:10.1371/journal.pone.0209326

5. Favaretto, A., Lazzarotto, A., Margoni, M. et al. Effects of disease modifying therapies on brain and grey matter atrophy in relapsing remitting multiple sclerosis. MultScler Demyelinating Disord ***3,*** *1 (2018).https://doi.org/10.1186/s40893-017-0033-3*

6. Pawate S, Wang L, Song Y, Sriram S. Analysis of T2 intensity by magnetic resonance imaging of deep gray matter nuclei in multiple sclerosis patients: effect of immunomodulatory therapies. J Neuroimaging. 2012 Apr;22(2):137-44. doi: 10.1111/j.1552-6569.2011.00622.x.Epub 2011 Jun 24. PMID: 21707826.

7. Preziosa P, Rocca MA, Pagani E, Storelli L, Rodegher M, Moiola L, Filippi M. Two-year regional grey and white matter volume changes with natalizumab and fingolimod. J NeurolNeurosurg Psychiatry. 2020 May;91(5):493-502. doi: 10.1136/jnnp-2019-322439. Epub 2020 Feb 28. PMID: 32111638.

8. Bernitsas E, Kopinsky H, Lichtman-Mikol S, Razmjou S, Santiago-Martinez C, Yarraguntla K, Bao F. Multimodal MRI Response to Fingolimod in Multiple Sclerosis: A Nonrandomized, Single Arm, Observational Study. J Neuroimaging. 2021 Mar;31(2):379-387. doi: 10.1111/jon.12824. Epub 2020 Dec 26. PMID: 33368776.

9. Bross M, Hackett M, Bernitsas MM, Bao F, Santiago-MartinezC,BernitsasE.Cortical surface thickness, subcortical volumes and disability between races in relapsing-remitting multiple sclerosis. MultSclRelatDisord 2021, in press

10. Sotirchos ES, Gonzalez-Caldito N, Dewey BE, Fitzgerald KC, Glaister J, Filippatou A, Ogbuokiri E, Feldman S, Kwakyi O, Risher H, Crainiceanu C, Pham DL, Van Zijl PC, Mowry EM, Reich DS, Prince JL, Calabresi PA, Saidha S. Effect of disease-modifying therapies on subcortical gray matter atrophy in

multiple sclerosis. MultScler. 2020 Mar;26(3):312-321. doi: 10.1177/1352458519826364. Epub 2019 Feb 11. PMID: 30741108; PMCID: PMC6689465.