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Changes in BDNF serum levels in patients with major depression disorder (MDD) after 6 months treatment with sertraline, escitalopram, or venlafaxine

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Abstract

Recent studies have implicated brain-derived neurotrophic factor (BDNF) in the pathophysiology of depression and the activity of antidepressant drugs. Serum BDNF levels are lower in depressed patients, and increase in response to antidepressant medication. However, how BDNF responds to different classes of antidepressant drugs is unknown. We assessed serum BDNF levels in 21 patients with major depressive episode treated with sertraline, escitalopram, or venlafaxine and 20 healthy controls. Serum samples were collected between 10 a.m. and 12 p.m. at baseline, 5 weeks, and 6 months of treatment. BDNF levels were measured via immunoassay. The severity of symptoms and response to treatment were assessed by the Hamilton rating scales for depression (HRSD). Baseline serum BDNF levels were significantly lower in depressed patients compared to controls. Sertraline increased BDNF levels after 5 weeks and 6 months of treatment. Venlafaxine increased BDNF levels only after 6 months. Escitalopram did not affect BDNF levels at either time point. A significant negative association was found between percentage increase in BDNF levels and percentage decrease in HRSD scores after 6 months of treatment. In conclusion, these results suggest that different antidepressant drugs have variable effects on serum BDNF levels. This is true even though the three different drugs were equally effective in relieving symptoms of depression and anxiety.

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Keywords

brain-derived neurotrophic factor (BDNF); neuroadaptation; depression; sertraline; venlafaxine; escitalopram

1. Introduction

Brain derived neurotrophic factor (BDNF) is a neurotrophin that has a pivotal role in regulating neuronal function across the life span (Bramham & Messaoudi, 2005). BDNF affects neuronal outgrowth, synaptic connectivity and neuronal repair (Lindsay et al., 1994; Lewin & Barde, 1996) and it is implicated in the regulation of activity-dependent synaptic plasticity (Escobar et al., 2003). Preclinical studies show that stress reduces the expression of BDNF in the hippocampus of rats (Altar, 1999; Duman & Monteggia, 2006), whereas in humans, BDNF has been implicated in the pathophysiology of psychiatric disorders, particularly major depression (D'Sa & Duman, 2002). A single bilateral direct infusion of BDNF into the hippocampus of rats has shown an antidepressant effect in animal models of depression, such as forced swim behavior (Shirayama et al., 2002). Patients with major depressive disorder (MDD) showed lower serum BDNF levels, which negatively correlated with depression rating scores (Karege et al., 2002a; Shimizu et al., 2003).

Chronic administration of antidepressant drugs or electroconvulsive treatment increase BDNF mRNA levels in rats (Nibuya et al., 1995). A growing body of evidence has associated the clinical latency of antidepressant drugs (Nestler et al., 2002) with the development of neuroadaptive changes involving neurotransmitter receptors, intracellular signaling molecules, transcription factors, and neurotrophins (Manji et al., 1991; Artigas et al., 1996; Popoli et al., 2001), including BDNF (Duman & Vaidya, 1998; Malberg et al., 2000; Duman et al., 1997). Preclinical studies have extensively investigated the effect of antidepressant treatment on BDNF regulation according to their pharmacological mechanisms and length of therapy. For example, fluoxetine administration has been found to induce a region-specific increase of BDNF mRNA in the hippocampus of rats after 14, but not 7 days of treatment (De Foubert et al., 2004). Moreover, BDNF protein levels were found to be increased only after 21 days with fluoxetine treatment in the pyramidal cell layer of CA2 and CA3 regions of the hippocampus of rats (De Foubert et al., 2004) but not before. Venlafaxine also produced a significant increase in BDNF mRNA in granular cell layer of hippocampus of rats after 7, 14, and 21 days of treatment; imipramine after 14 and 21 days whereas fluoxetine had no effect on BDNF mRNA, after neither short- nor longer-term (Larsen et al., 2007). The effect on BDNF appears to be variable depending on the brain region, the cell type, length of treatment and the pharmacological characteristic of the drug. Preclinical studies have shown that serum BDNF concentrations have been positively related to cortical BDNF levels (Karege et al., 2002b). Therefore, it is likely that changes in serum BDNF levels may reflect changes in BDNF production and/or clearance in the brain. In humans, several classes of antidepressant medications with different mechanisms of action have been shown to increase serum BDNF levels after short and intermediate duration of treatment (Gervasoni et al., 2005; Huang et al., 2007; Gonul et al., 2005; Yoshimura et al., 2007; Aydemir et al., 2005; Altar, 1999; Piccinni et al., 2008) in patients with MDD. However, the differential effects of antidepressants on BDNF peripheral levels based on pharmacological profile are unknown.

The aims of this study were to: (1) compare serum levels of BDNF in depressed patients versus normal controls; (2) test the action of three different antidepressant drugs (sertraline, escitalopram, and venlafaxine) on serum BDNF levels after 5 weeks and 6 months; and (3)

test the association between BDNF serum levels and rating scores for depression after treatment.

2. Materials and Methods

2.1 Sample and Treatment

The study protocol was carried out in accordance with the latest version of the declaration of Helsinki and the study design was reviewed by an appropriate ethical committee at University of Rome “La Sapienza”, “Sant’Andrea” Hospital. All subjects provided written informed consent. 21 study subjects, 11 males and 10 females aged 18-64 years who met diagnostic criteria for major depressive episode (MDD) (DSM-IV-TR, American Psychiatric Association., 2000) and 20 normal volunteer controls, 9 males and 11 females entered the study. All participants were evaluated by two expert psychiatrists at the Department of Psychiatry and Psychological Medicine, University of Rome “La Sapienza”, “Sant’Andrea” Hospital between September 2003 and September 2005. Study subjects did not receive any antidepressant or antipsychotic treatment for at least a month prior the onset of the treatment. None of the patients had a history of electroconvulsive therapy or transcranial magnetic stimulation treatment. Patients were free of other psychotropic drugs except that benzodiazepines were allowed. Control subjects were enrolled in June, 2005 and were free of a history of any DSM-IV Axis I or II disorder, major physical illness, alcohol or drug abuse and dependence. Control subjects had not received any medication with psychotropic drugs in the preceding 5 years.

Study subjects at baseline were randomized to sertraline (50-200 mg/day), venlafaxine (75-225 mg/day) and escitalopram (10-20 mg/day) treatment for 6 months. Blood samples of study subjects were collected at baseline (1 day prior to the start of drug treatment), and after 5 weeks and 6 months of treatment. Blood samples of control subjects were taken once.

The severity of depression was assessed by trained raters by means of the Hamilton Depression Scale (HRSD) (Hamilton, 1960) and symptoms severity was defined as follows: HRSD scores= remission 7; mild depression 7-17; moderate-severe depression 17 (Endicott et al., 1981). The clinical assessment was done at baseline, 5 weeks and 6 months.

2.2 Assessment of serum BDNF levels

Serum samples from patients and controls subjects were collected between 10 am-12 p.m. and stored at -20° C. Blood (4 ml) was sampled in anticoagulant-free tubes and kept at room temperature for 1 h followed by 1 h at 4° C (for platelet activation) before the serum was isolated (centrifugation at 2,000 g for 10 min at 4° C). Serum BDNF protein content was measured by ELISA using a commercially available kit (BDNF Emax Immunoassay System, Promega, Italy). 96-well plates were coated with anti-BDNF monoclonal antibody and incubated at 4° C for 18 h. Plates were incubated in a blocking buffer for 1 h at room temperature. Samples and BDNF standards were shaken at room temperature for 2 h, followed by washing with the appropriate washing buffer. The plates were incubated with anti-human BDNF polyclonal antibody at room temperature for 2 h, extensively washed, and incubated with anti-IgY antibody conjugated to horseradish peroxidase for 1 h at room temperature. The plates were incubated in peroxidase substrate and tetramethyl-benzidine solution to produce a color reaction. The reaction was stopped with HCl (1.0 M) and the optical density of each well was measured at 450 nm using an Emax plate reader. All samples were assayed in duplicate. Samples were analyzed after 12 months (Trajkovska et al., 2007) from collection.

3. Statistical analysis

For the comparison of demographic and baseline characteristics among the three treatment groups, Kruskal-Wallis statistics were used for continuous variables and Chi-square statistics were used for categorical variables. Wilcoxon rank-sum statistics were used for the comparison of treated patients and control subjects. Exact p-values were calculated when any group has sample size less than 10. For the comparison of treatment effects on BDNF levels over time, we used a mixed effect model with BDNF, main effects Time, Treatment, and Time x Treatment interactions. Gender, Age, baseline BDNF, baseline HRSD score were entered as covariates to reduce confounding effects and the spatial power covariance structure was used to model the correlations between repeated measures from the same subject. We compared effect of treatments on HRSD scores at each time period using Mantel-Haenszel chi-square test and estimated exact p-values. To assess the correlations between percent changes in BDNF and percent changes in HRSD scores, we used Spearman correlation coefficients. The association between percent change in BDNF and baseline HRSD scores was tested using linear regression with change in BDNF as outcome and baseline HRSD as predictor. For these analyses, we did not correct for multiple comparisons, a p-value of less than 0.05 was considered statistically significant. Although multiple tests results were examined, each parameter was of interest in its own, so we chose to report all individual p-values and make separate statements in relation to our hypotheses. When multiple test results have implications on specific responses, correction for multiple comparisons is not needed, as it is more relevant to know the strength of evidence for testing individual hypotheses (Cook & Farewell, 1996). All analyses were performed using SAS for Windows (Version 9.1.3, SAS Institute, Cary, NC).

4. Results

4.1. Sample

Demographic and clinical characteristics of the study sample (n=21) and healthy controls (N=20) are given in Table 1. At baseline, there were no significant differences between the three different antidepressant treatment groups with respect to gender distribution, age, BDNF serum levels, and HRSD scores, duration of illness, number of previous episodes and comorbidity. A significant difference between the study and control group was observed for age (study group= 42.4 ys $\pm$ 8.0; controls=31.8 ys $\pm$ 5.9; p=0.0003) and BDNF levels (study group= 35.4 $\pm$ 15.2 ng/mL; control group= 64.1 $\pm$ 13.1 ng/mL; p<0.0001). After titration, the dose of antidepressants was maintained stable throughout the study. The mean $\pm$ SD daily doses for sertraline, venlafaxine, escitalopram were 96.4 $\pm$ 50.8 mg; 150 $\pm$ 61 mg; 16.4 $\pm$ 3.8 mg, respectively. None of the study subjects dropped out from the study.

4.2. Analysis of BDNF changes after treatment

Baseline, 5 weeks, 6 months BDNF levels are given in Table 2. A significant time (F=9.55; DF=2/35, p=0.0005) and time x treatment interaction (F=6.35; DF=4/35, p=0.0006) with age, gender, baseline BDNF and HRSD scores as covariates was observed for BDNF levels. Overall comparison showed significantly different BDNF serum levels between treatment groups after 5 weeks (F=10.5; DF=2/35, p=0.0003) and 6 months treatment (F=8.6; DF=2/35, p=0.0009) (see Table 2). For sertraline-treated patients, a significant increase in BDNF levels was observed after 5 wks (diff= -21.1; t=-3.7; p=0.0006) and 6 months (diff= -22.8; t=-3.9, p=0.0003). For venlafaxine-treated patients a significant increase in BDNF levels was noticed after 6 months treatment (diff= -22.6; t=-3.9; p=0.0004) but not 5 weeks. No significant increase in BDNF levels was noticed among individuals treated with escitalopram at any time point.

The pairwise comparison for changes with baseline BDNF values, HRSD scores, gender and age as covariates showed higher serum levels of BDNF for the sertraline-treated patients when compared to venlafaxine treatment group after 5 weeks (diff= 23.5; ES= 4.1; $p=0.0003$) but not after 6 months; whereas, the sertraline-treatment group showed higher levels of serum BDNF when compared to escitalopram both at 5 weeks (diff= 23.2; ES= 3.8; $p=0.0005$) and 6 months (diff= 21.9; ES= 3.6; $p=0.001$). Moreover, significant differences between venlafaxine-, and escitalopram-treated patients were observed at 6 months (diff= 22.4; ES= 3.7; $p=0.0007$) but not at 5 weeks favoring venlafaxine with greater values of serum BDNF.

A secondary analysis was performed to evaluate the persistence of a significant time effect also when the three treatments were grouped together ($N=21$). In fact, the results showed a significant time effect ($F=6.13$; $DF=2/39$; $p=0.005$) due to a significant increase in BDNF at 6 months when compared to baseline ($t=-3.4$; $DF=39$; $p=0.002$) and at 6 months when compared to 5 weeks ($t=2.43$; $DF=39$; $p=0.02$).

4.3 Changes of HRSD scores after treatment

Baseline, 5 weeks, 6 months symptoms severity and percentage of remission for HRSD scores were given in Table 2a. Comparison using Mantel-Haenszel chi-square test did not show any significant difference in symptoms severity between the three treatment groups at baseline. At 5 weeks, the three different treatment groups showed similar proportions of patients meeting remission criteria ($p=0.09$) and at 6 months everyone was remitted.

4.4. Correlations between percentage change in BDNF levels and percentage change in HRSD scores after treatment

When the study group was considered as a whole ($N=21$), a significant negative association ($\rho=-0.5$, $p=0.008$) between percentage change in BDNF levels and percentage change in HRSD score was observed after 6 months treatment but not after 5 weeks. No association between severity of depressive symptoms at baseline and percentage increase in BDNF levels at 5 weeks and 6 months were observed. No further analyses were conducted within each treatment group due to small sample size.

5. Discussion

BDNF levels were significantly lower in depressed patients at baseline relative to normal controls. This result confirms several reports on how patients with depressive episode show lower levels of BDNF serum concentrations when compared to healthy controls (Gervasoni et al., 2005; Yoshimura et al., 2007; Gonul et al., 2005; Aydemir et al., 2005; Piccinni et al., 2008). Moreover, our results indicate a significant increase in BDNF serum levels after 5 weeks of treatment with sertraline and after 6 months of sertraline and venlafaxine. These findings corroborate the results of Gervasoni (Gervasoni et al., 2005), which showed a significant increase in BDNF serum levels after 13 weeks (± 6 weeks) mean duration of antidepressant treatment with SSRI or tricyclic antidepressants in 26 patients with unipolar or bipolar depression. Similar results were reported by Gonul (Gonul et al., 2005) who observed a significant increase in serum BDNF levels after 8 weeks treatment with venlafaxine, sertraline, fluoxetine and paroxetine in 33 patients with major depressive disorder, and Huang (Huang et al., 2007) who confirmed the increase in serum BDNF levels in 61 patients after 4 weeks of treatment with fluoxetine, paroxetine, venlafaxine and mirtazapine.

Few studies have reported the long-term effects of antidepressants on BDNF in depressed patients. Aydemir (Aydemir et al., 2005) showed increase in serum BDNF peripheral levels

in ten patients with major depression after 3 months of treatment with venlafaxine; and Piccinni (Piccinni et al., 2008) reported, in a 12 months prospective study, an increase in BDNF peripheral levels in 15 depressed patients treated with SSRI and tricyclic antidepressants. Our data also suggest that with sertraline and venlafaxine, the effects on peripheral BDNF are sustained over time. This is consistent with the possibility that BDNF plays an important role in the maintenance of antidepressant action.

The other main finding of our study focuses on the differences among sertraline, venlafaxine and escitalopram with respect to BDNF serum changes. The increase in BDNF serum levels has been observed at 5 weeks ($LSM=+ 21.1 \pm 5.6$ ng/ml) after sertraline treatment. This increase maintained similar magnitude at 6 months ($LSM=+ 22.8 \pm 5.8$ ng/ml). The venlafaxine-treated patients showed an increase in BDNF serum levels at 6 months ($LSM=+ 22.6 \pm 5.8$ ng/ml) but not at 5 weeks ($LSM=-3.1 \pm 5.6$ ng/ml). Sertraline treatment almost normalized serum BDNF levels in depressed patients after 5 weeks and 6 months, whereas venlafaxine showed a significant impact on BDNF serum levels only after long-term treatment. These findings are in accordance with the ones from Yoshimura (Yoshimura et al., 2007) who observed an increase in BDNF serum levels in 42 patients with major depression episode after 8 weeks of treatment with milnacipran, another serotonergic/noradrenergic reuptake inhibitor like venlafaxine, but not 4 weeks. No significant increase in BDNF values were noted for escitalopram treated patients at either time point ($LSM=-5.8 \pm 5.6$ ng/ml; $LSM=-2.8 \pm 5.8$ ng/ml). This result is in contrast with the one reported by Aydemir et al. (2006), who found an increase in BDNF serum levels in 20 women affected by major depression after 6 weeks of treatment with escitalopram. Our escitalopram treated group counted 4 females and 3 males, the very small sample size did not allow any further statistical inquiry; gender differences in our sample might have contributed to the different outcome. However, at baseline a higher proportion of escitalopram-treated patients were mildly depressed and the mean baseline BDNF levels for escitalopram group were higher (44.4 ± 16.4 ng/ml) as compared to the other groups (see Table 2). These differences were not significant, although this may be attributable to the small sample sizes. It is notable, however, that the BDNF levels in the escitalopram group were somewhat lower after 5 weeks and 6 months of treatment than the other groups.

The different timing in BDNF increase shown by the sertraline- and venlafaxine-group despite the prompt response to treatment seen in both groups might be related to the differential effect exerted by the two drugs on the multitude of molecular mechanisms that contribute in BDNF production. In fact, preclinical studies have shown that different classes of antidepressants have varying effects on BDNF transcription, release, activation of receptors and secondary messengers. For example, duloxetine, another serotonergic/noradrenergic reuptake inhibitor, has been shown to affect BDNF mRNA levels in different brain regions of rats according to the length of treatment. For instance, chronic administration (3 weeks) of duloxetine increased levels of BDNF mRNA in the prefrontal, entorhinal and parietal cortex, but not in the hippocampus; acute (single i.p. injection) administration did not produce any significant change (Calabrese et al., 2007). These results are confirmed by Mannari (Mannari et al., 2008) who recently showed that chronic but not acute administration of duloxetine produced an increase in total BDNF in the prefrontal cortex of rats; only chronic high doses of duloxetine increased total BDNF levels in cerebrospinal fluid of rodents while repeated administration of duloxetine, even at the highest concentration, was not able to change total BDNF levels, either in the serum or the plasma. Moreover, acute and chronic treatment with fluoxetine, citalopram, clomipramine, imipramine, reboxetine and moclobemide has been tested in mice on TrkB protein levels and TrkB autophosphorylation. TrkB is a high affinity receptor for BDNF and its autophosphorylation results in activation and serves as an indirect signal of BDNF neuronal release (Rantamaki et al., 2007). All the antidepressants significantly increased TrkB

autophosphorylation in the anterior cingulate cortex and hippocampus of mice within 30-60 min of a single injection but none of the acute treatments influenced the expression levels of total TrkB protein (Rantamaki et al., 2007). The reported evidence show how BDNF serum concentrations are variously subjected to an intricate and complex cascade of molecular mechanisms where the length of treatment along with different pharmacological profile of the drug might act a crucial role depending on the cellular or subcellular domain studied. Sertraline affinity for σ_1 -receptor might also explain the rapid action in increasing BDNF serum levels (Lowther et al., 1995). Interaction with σ_1 -receptors has also been demonstrated for venlafaxine in a preclinical study; the effects of venlafaxine on the forced swim test in rats were counteracted by a σ_1 - antagonist (Dishir et al., 2007). Sigma-receptors were first described as opiate receptors, but this was ultimately was disproven. Sigma agonists have been shown to possess antidepressant properties, which may occur via modulation of serotonergic transmission (Bermack & Debonnel, 2001). No σ_1 -receptor affinity has been demonstrated for escitalopram (Fabre & Hamon, 2003), instead a recent study showed how escitalopram increased BDNF and TrkB mRNA levels in the hippocampus and prefrontal cortex of juvenile rats after four days of treatment (Kozisek et al., 2008). This finding illustrates how also a highly selective serotonin reuptake inhibitor, is able to produce significant changes in BDNF.

Our results related to the escitalopram-treated group appear to be in contrast with recent preclinical and clinical findings; a bigger sample size, an accurate selection of the study group based on the elicitation of possible gender differences and the detection of BDNF both in serum and in whole blood where the measurement appears to be more accurate (Trajkoska, 2007) are warranted to further expand actual knowledge on BDNF increase in escitalopram-treated patients.

All three antidepressants were highly effective in relieving depression symptoms both after 5 weeks and 6 months (Rabkin & Klein, 1987), despite their different effects on serum BDNF levels. . This finding raises the question of whether changes in BDNF levels are relevant to the clinical effects of antidepressants and whether they can be considered reliable predictors of antidepressant response. On the other hand, there was a significant association between the increase in BDNF serum levels and the decrease in HRSD scores at endpoint, indicating that a higher percentage increase of BDNF serum levels correspond to a clinical remission from depressive symptoms. A broader clinical assessment with follow-up data is needed to test this question.

A few limitations should be kept in mind when evaluating these results. First, the sample sizes were relatively small, which may have limited our ability to determine meaningful differences and we would consider these results preliminary until replication. Further, the symptom assessments were limited to HRSD and may have missed important components of the depressive syndrome. Lastly, the difference in age between the control and the study group with an older age for this latter might have affected the baseline BDNF values, although the statistical analysis was corrected for BDNF values at baseline, still this result might constitute a confounding factor when interpreting the results at baseline. The younger age of the healthy controls might explain the higher BDNF levels at baseline since it has been reported that there's a negative correlation between median values of plasma BDNF levels and age in healthy humans (Lommatzsch et al., 2005). Indeed, the role of aging in healthy adults on neurotrophic factors needs further research.

In conclusion, our study corroborates the existing literature on the positive increment of BDNF serum levels after a long-term treatment with antidepressants and it adds valuable though still preliminary knowledge to the interesting issue of the differential effect of three different antidepressants on BDNF serum levels.

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Table 1

Baseline demographic and clinical characteristics of patients randomized to sertraline, venlafaxine and escitalopram treatment.

	Sertraline	Venlafaxine	Escitalopram	Comparison of Treatment Groups (p-values)	Controls	Comparison of Treatment vs. Controls (p-values)
Number of patients	7	7	7	NS	20	NS
Age (yrs) Mean (SD)	42.4 (7.5)	43.7 (9.5)	41.3 (7.9)	NS	31.8 (5.9)	0.0003
Gender, no.						
Male	4	4	3	NS	9	NS
Female	3	3	4	NS	11	NS
BDNF (ng/mL), Mean (SD)	29.4 (12.6)	32.3 (14.0)	44.4 (16.4)	NS	64.1 (13.1)	<0.0001
Duration of illness yrs, Mean (SD)	10.7 (4.1)	11.6 (4.9)	14.2 (2.9)	NS	N/A	N/A
Previous Episodes	None	None	None	NS	N/A	N/A
Comorbidity	None	None	None	NS	N/A	N/A
HRDS scores , Mean (SD)	19 (5.3)	19.4 (4.5)	14.3 (5.9)	NS	NA	N/A

Legend: N/A=not/applicable; NS: Not Significant at Alpha = 0.05; SD= Standard Deviation

Table 2

BDNF levels at baseline, 5 weeks, 6 months.

Parameter (Mean $\pm$ SD)	Sertraline	Venlafaxine	Escitalopram	Overall Comparison (p-value)	Sertraline vs. Venlafaxine (p-value)	Sertraline vs. Escitalopram (p-value)	Venlafaxine vs. Escitalopram (p-value)
BDNF ng/mL							
Baseline	29.4 (12.6)	32.2 (14.0)	44.4 (16.4)	NS	NS	NS	NS
5 wks	50.6 (14.2) ***	29.1 (16.3)	38.6 (14.4)	0.0003	0.0002	0.0006	NS
6 mo	52.3 (12.7) ***	54.9 (12.2) ***	41.6 (14.1)	0.0009	NS	0.001	0.0008

Legend: N/A=not/applicable; NS: Not Significant at Alpha = 0.05; Changes from baseline are reported with p-values: * <0.05; ** <0.01; *** <0.001.

Table 2a

Symptoms severity and percentage of remission by HRSD scores at baseline, 5 weeks, 6 months.

Parameter	Sertraline			Venlafaxine			Escitalopram			Overall (p-value)
	HRSD	7	17	HRSD	7	17	HRSD	7	17	
Symptoms severity (%)										
Baseline	0	42.9	57.1	0	28.6	71.4	0	85.7	14.3	NS
5 wks	57.1	42.9	0	14.3	0	0	100	0	0	NS
6 mo	100	0	0	0	0	0	100	0	0	NS

Legend: N/A=not/applicable; NS: Not Significant at Alpha = 0.05