Simultaneous Use of Immunoglobulin with Natalizumab Attenuates the JCV Stratify Index Elevation- a 2 Year Analysis

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OBJECTIVES

To assess whether combined use of immunoglobulin with NTZ alters Stratify index.

BACKGROUND

•The incidence of progressive multifocal encephalopathy (PML) in Multiple Sclerosis (MS) increases exponentially with prolonged Natalizumab (NTZ) use.

•JCV Stratify (Stratify) is a sensitive test, but lacks specificity to determine NTZ course of action.[1]

•Use of immunoglobulin (IgG) in the treatment of MS is controversial.

•Off label immunoglobulin use has been limited to patients who are steroid non-responders, patients who have proven refractory to steroids because of prolonged use, or in whom steroids are contraindicated.

METHODS

•Subjects included MS patients (n = 36) enrolled in the Touch Program and treated with NTZ for 2 years.

•Baseline Expanded Disability Status Scale (EDSS) scores ranged from 2.0-8.0.

•Subjects were divided into 2 groups:

1. Receiving immunoglobulin/NTZ (n =20)
2. Receiving NTZ alone (n =15).

•Patients were evaluated with monthly blood testing, monthly neurological examination, and annual magnetic resonance imaging (MRI) scans.

•JCV DNA PCR probes in whole blood and urine as well as Stratify testing were performed initially and every 6 months.

•NABs to NTZ were obtained at times of exacerbation.

•MS exacerbations were treated with 3 day courses of solumedrol or ACTHar gel.

•NTZ was administered at a dose of 300 mg IV q 28 days and those receiving IgG received 40 gm q month.

RESULTS

•All patients remained neurologically stable with respect to EDSS scoring throughout the study.

•2 MS patients had exacerbations, one of which was treated with solumedrol and the other with ACTHar gel.

•No patient developed PML.

•There was no correlation between Stratify and DNA PCR probe determination in whole blood and urine over the two year interval.

Table 1: Baseline Demographics

Variable		n	(%)
Age		41.4	±13.2
Gender			
	Male	16	(44.4)
	Female	20	(55.6)
Race			
	White	20	(55.6)
	Black	8	(22.2)
	Asian	1	(2.8)
	Hispanic	7	(19.4)
Tx			
	IGG/NTZ	21	(58.3)
	NTZ	15	(41.7)

Table 2: Clinical Outcomes

Outcomes	n (%)
MS patients with exacerbations	2 (5.6%)
% exacerbation free	94.4%

Figure 1: Patient Outcomes at 2 years by Therapy

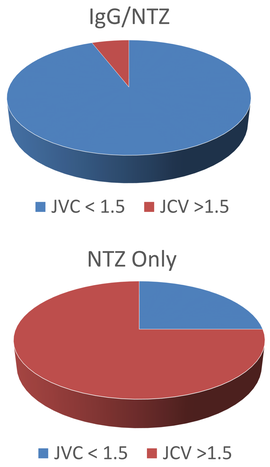
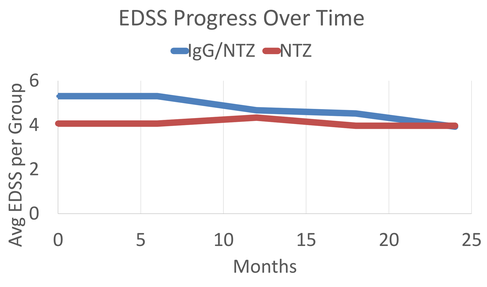


Figure 2: Average EDSS Progress based on the Treatment Type



Observations throughout the Study

•There was no correlation between Stratify and DNA PCR probe determination in whole blood and urine over the two year interval.

•In the combination therapy group 60% (n = 12) and in the NTZ group 40% (n = 6) had Stratify indices greater than 1.5

•Patients receiving immunoglobulin had a decline of Stratify index noted initially at the 6th month (n = 4; 20%) and continued (n=16; 80%) throughout the duration of the study.

•Those patients not receiving immunoglobulin continued to display Stratify indices that were elevated above initial baseline readings.

•Over the 2 year interval, EDSS scores improved (n= 10; 50%) in those on combination therapy and (n=6; 40%) on NTZ.

•6 MS patients (6%) remained Stratify negative throughout the study.

•MRI data revealed an increase in T2 burden in both groups.

Figure 3: Normal Distribution of Change in EDSS over 2 year period

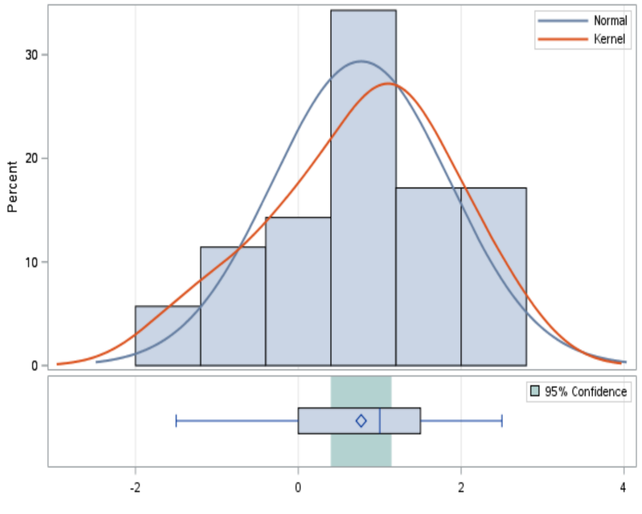
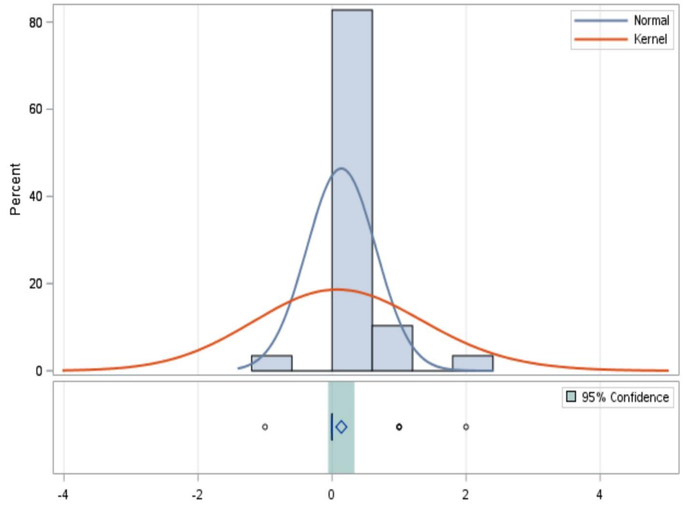


Figure 4: Normal Distribution of Change in ELISA over 2 year period



DISCUSSION

•Although there is a trend showing difference between IgG/NTZ and NTZ treatments, the difference does not appear to be significant

•Possible causes for lack of significance does not indicate a lack of relationship, instead this could be caused by the relatively small sample size of participants

•One important aspect in the study is the consistency in the trends between the two therapies throughout the 2 year period

CONCLUSION

•The immunomodulating effect of IgG is reflected in the disparities of Stratify index in those on combination therapy versus NTZ alone.

•The study continues to emphasize that Stratify is sensitive but not specific in determining NTZ use.

•The study suggests that the concomitant use of IgG with NTZ lessens elevations in Stratify index and may attenuate development of PML.

•The study may also point to a potential for decrease in risk for secondary autoimmune conditions that are associated with the use of other disease specific agents and various comorbidities linked with treatment.

REFERENCES

1. Bailey RO, Garcia MV, Sprague CG. Stratify JCV Antibody ELISA Test: Who gets What? Issues of Sensitivity versus Specificity. International Journal of Multiple Sclerosis Care. 18: (Suppl. 1) p. 17, 2016.

Statistical Analysis: Simple descriptive statistics were done using SAS 9.4 and Excel, Cox Proportional Hazards survival model was performed using SAS 9.4 and Software R.

Cox Proportional Hazards:

The Cox model estimates the survival probability S(t) of a patient surviving at least until time t, $S(t) = \Pr(T > t)$

via the hazard function defined by:

$$\lambda(t) = \lim_{dt \to 0} \frac{\Pr(t \le T < t + dt)}{dt \cdot S(t)} = \frac{f(t)}{S(t)} = -\frac{S'(t)}{S(t)}.$$

The hazard function is modeled as a function of input variables (e.g., EDSS score) via the equation:

$$\lambda(t|X) = \lambda_0(t)\exp(\beta_1 X_1 + \cdots + \beta_p X_p) = \lambda_0(t)\exp(\beta' X).$$

Disclosure:
The authors have nothing to declare