DX 4209

Stratify JCV Antibody ELISA Test: Who Gets What? Issues With Sensitivity Versus Specificity

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Objective

- To assess whether Stratify JCV antibody ELISA test (Stratify) should be used as a "gold standard" to determine initiating or continuing Natalizumab (NTZ) therapy in multiple sclerosis patients.

Background

- Since the inception of use of Stratify as a safeguard to predict potential development of progressive multifocal leukoencephalopathy (PML), there has been considerable reservation about the use of NTZ in seropositive patients or seroconverters.
- Stratify indices of greater than 1.5 are felt to carry more significance.
- Stratify may provide a false sense of security in predicting probability of PML in patients considered candidates for NTZ therapy.

Methods

- 45 MS patients were followed over a period of 2 to 9 years.
- Baseline EDSS scores ranged from 2.0-7.0 and were followed serially.
- Every patient received monthly peripheral blood work, including CD4/CD8 ratios.
- Per TOUCH protocol, yearly brain, cervical, and thoracic (when appropriate) MRI scans.
- Stratify every six months. Additionally, JCV DNA PCR in whole blood, CSF, and urine were taken yearly to compare with Stratify results.
- In the end, comparison was made with clinical examination, MRI scanning, Stratify, JCV DNA PCR in whole blood, urine, CSF, EDSS scoring, and relapse rate while on NTZ.
- Using SAS, a generalized linear mixed regression model was used to estimate the odds ratio.

Results

- No correlation between NTZ treatment duration and the development of Stratify positivity.
- All Stratify positive patients were negative when compared to DNA PCR (2%) who were also Stratify positive.
- 2 patients withdrew from the study (one at 3 years and one at 5 years) because of more frequent MS relapses despite negative NABs to NTZ.
- One patient developed positive conversion of whole blood DNA PCR (2%) who was also Stratify positive.
- Two patients had DNA PCR positive seroconversion in urine (4%).
- No patient developed DNA PCR positive seroconversion in CSF.
- No patient developed PML.
- Monthly CD4/CD8 ratios, CD4% helper T-cells, and CD8% suppressor T-cell levels in NTZ treated patients remained stable without evidence of peripheral immunosuppression throughout the entire duration of the study.
- 2 patients with elevated indices converted from positive to negative (4.4%) after having been on NTZ for greater than 3 years.

Table 1. Study Population Demographics and Baseline Data

	Study Subjects (n=45)		Dropout (n=2)	
	Mean	Range	Mean	Range
Age (yrs.)	48.2	25-79	33	32-34
EDSS	3.5	2-8.5	4.0	3.0-5.0
Duration Rx. NTZ (yrs.)	6.0	5.0-9.0	5.0	4.0-6.0
Adjunctive Rx. IV IgG (10)	1.0	0.5-1.5	-	-
Adjunctive Rx. ACTHar Gel (5)	240	240	-	-
Female / Male	28/17	-	2/0	-
Disease Duration (yrs.)	10	5-32	6	5-7

***August 2011, 1st generation JCV antibody assay was made available outside of the Stratify Clinical Trial program. The second generation was launched on January 2013.**

Figure 1. Patients on NTZ

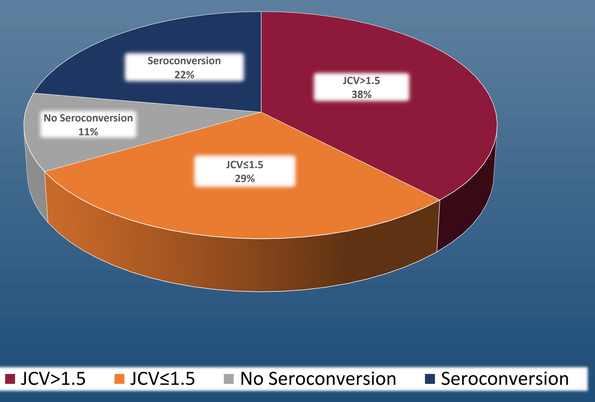
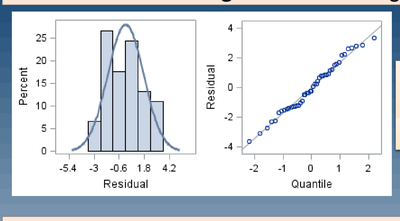


Figure 2. Modeling of DNA Tests



Odds Ratio	95% Wald Confidence Interval	
2.45	0.11	53.71

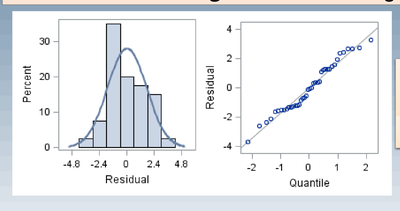
Table 2. Sensitivity and Specificity on DNA Test

Table of DNA by EDSS

DNA	EDSS: Low	EDSS: High	
(-)	20	23	43
(+)	1	1	2
	21	24	45

Sensitivity	Specificity
0.0417	0.9524
PPV	**NPV**
0.5000	0.4651

Figure 3. Modeling of ELISA Tests



Odds Ratio	95% Wald Confidence Interval	
0.49	0.08	3.10

Table 3. Sensitivity and Specificity on ELISA Test

Table of ELISA by EDSS

ELISA	EDSS: Low	EDSS: High	
(-)	3	6	9
(+)	18	18	36
	21	24	45

Sensitivity	Specificity
0.7500	0.1429
PPV	**NPV**
0.5000	0.3333

Conclusion

- Although Stratify may be a sensitive test, it offers little in terms of specificity to predict possible occurrence of PML in NTZ treated patients and did not render specificity for determining NTZ therapy.
- The use of Stratify testing may hamper treatment of MS patients who would otherwise have had considerable clinical benefit, and should not be listed as a sole measure in therapeutic decisions.
- The study enumerates a more elaborate strategy for PML risk identification. Stratify may serve as a biomarker, yet there is a need for alternative assessments when considering the use of NTZ.

References

- Bailey R., Nguyen V., Sprague C. Use of ACTHar Gel for Multiple Sclerosis Exacerbations during Natalizumab Induction and Maintenance. Int J of MS Care. 2013; 15 (suppl 3):83

Acknowledgement

The authors have nothing to declare