Investigating Functional Differences in NT5c1A Seropositive and Seronegative IBM Participants in the INSPIRE-IBM Trial

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Objective

To explore the differences in severity of motor function between individuals with NT5c1A seropositive and seronegative inclusion body myositis (IBM)

Introduction

IBM is a subtype of the idiopathic inflammatory myopathies characterized by muscle weakness and inflammation afflicting patients over the age of 40 years, with a mean decline in strength of 3.5% and 5.4% per year on manual muscle testing and quantitative muscle testing, respectively[1]. Anti-NT5c1A antibodies are common in patients with IBM, thus becoming a novel biomarker for diagnosis. While the relation between motor function severity and serological status of IBM patients is still largely unknown, a previous study suggested that NT5c1A seropositivity may prognosticate a more severe IBM phenotype, though this study was limited by a small sample size[2]. Another study suggested IBM patients with more severe muscle weakness were more likely to be anti-NT5c1A positive in the univariable analysis, but this was not statistically significant in the multivariable analysis[3]. Correspondingly, an exploratory study with a cohort of 311 patients observed differences in clinical features between NT5c1A antibody positive and negative patients, potentially highlighting a distinct IBM subtype with a more severe phenotype[4]. However, a recent study reported no significant clinicopathologic differences among patients who were seropositive for anti-NT5c1A antibody from seronegative patients, though seropositive IBM patients showed more frequent involvement of finger flexion weakness[5]. This preliminary data furthers motivation to revisit the examination of clinical features in IBM patients while stratifying for serological status and disease duration.

Design/Method

INSPIRE-IBM is the largest prospective natural history study involving 150 participants from a consortium of thirteen myositis treatment centers across the United States. Functional assessments are administered at each visit, which is every six months over two years. Participants performed serum blood samples to evaluate for NT5c1A antibody status and were stratified based on serological status. Individual sites and investigators were blinded to serology results. Out of 150 participants, antibody results and functional assessment data was available for 140 patients. This analysis involves results from the Baseline visit of the enrolled participants.

Functional Assessments include:

Manual muscle testing (MMT) is a scored neurological examination. This test is performed by blinded clinical evaluators on the following muscle groups for enrolled participants: bilateral shoulder abductors, elbow flexors, elbow extensors, wrist flexors, wrist extensors, hip flexors, hip abductors, knee flexors, knee extensors, ankle dorsiflexors, and plantar flexors, plus neck flexors. Each muscle is scored 0 to 5, with 0 representing paralysis and 5 is normal strength. Modifications to this scale are represented by either a plus or minus score, allowed for scores 3 and above. Scores with +/- were converted into numerical values 0-5 (3=3, 3+=3.33, 4-=3.67, 4=4, etc.) and scores were summed to get a total out of 120.

The Timed Get Up and Go (TUG) is used to assess a person's ability and amount of time to rise from a seated position to standing, walk 3 meters, turn around and return to the chair and sit. No physical assistance is given but participants may hold the chair so that it doesn't move.

Inclusion Criteria:
- Age 40 years and older
- Fulfills ENMC 2011 Criteria for diagnosis of IBM
- Disease Onset is within 10 years of baseline visit

Exclusion Criteria:
- Current/ recent use of immunomodulation/immunosuppression therapy
- Current/ recent use of investigational medication or therapy
- Co-existing significant medical or surgical conditions that would influence study participation or alter natural history.

Results

NT5c1A Antibody Status	Number of Subjects
Seropositive	69 (48%)
Seronegative	71 (51%)
Total	140

Table 1: Antibody results from 140 participants identifying the number of seropositive and seronegative patients.

Results

Test	0-3 Yr. Avg (SD)	4-6 Yr. Avg (SD)	7-10 Yr. Avg (SD)	F-Stat	P-Value
TUG Velocity	0.533 (0.323)	0.464 (0.256)	0.382 (0.26)	2.799	0.064
MMT Total	99.766 (9.190)	94.327 (11.215)	89.716 (12.367)	5.831	**0.004**

Table 2: Results of ANOVA tests comparing the average TUG velocity and total MMT between disease duration groups. A significant p-value indicates that at least one disease duration group has a statistically significant difference in mean functional assessment score.

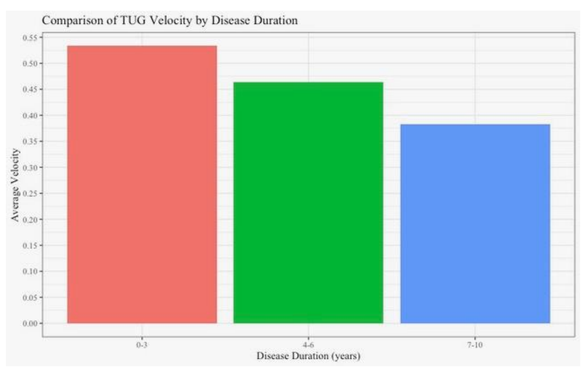

Figure 1. Comparison of TUG velocity by disease duration.

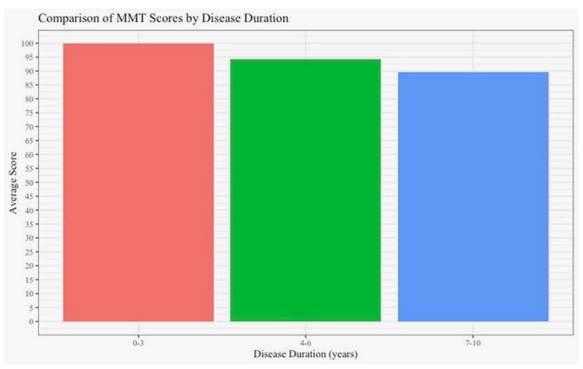

Figure 2. Comparison of MMT scores by disease duration.

Test	Seropositive Average	Seronegative Average	95% CI	P-Value
TUG Velocity	0.415	0.394	(-0.081, 0.400)	0.690
MMT Total	91.343	93.711	(-6.424, 1.687)	0.249

Table 3: Results of two-sample t-tests comparing the average TUG velocity and total MMT score between seropositive and seronegative subjects.

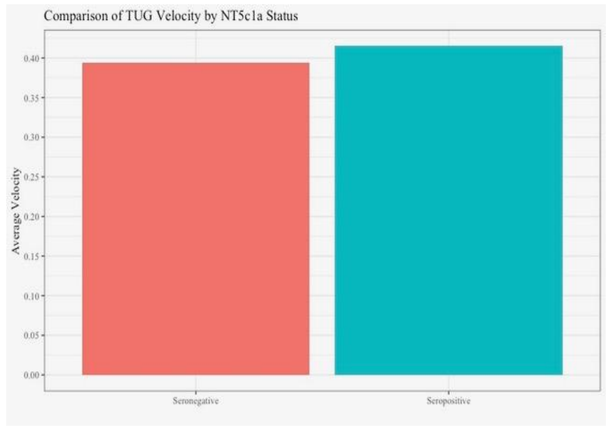

Figure 3. Comparison of TUG velocity between the seropositive and seronegative groups.

Figure 4. Comparison of MMT scores between the seropositive and seronegative groups.

Conclusion

In summary, these results highlight the need to further investigate the hypothesized relationship between NT5c1A antibody status and functional severity. Distinctively, there was a statistically significant difference in at least one of the disease duration subgroups with respect to the mean MMT scores, which is not only compatible with previous findings but are consistent with notable clinical features of the disease[1]. Compatibly, this trend is observed through TUG velocity scores and disease duration subgroups, though not statistically significant. These findings show the TUG velocity average for the seropositive group are slightly higher on average than the seronegative group; however, the MMT mean scores for the seropositive group are slightly lower on average than the seronegative group. Overall, these results should be cautiously interpreted considering previous conflicting reports involving the potential phenotypical differences between seropositive and seronegative IBM patients, furthering the need to explore the controversy.

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