

Competitive Inhibition of Myostatin in the Management of Sarcopenia and Muscle Wasting Disease: Implications for Primary Progressive Multiple Sclerosis

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OBJECTIVES

- The objective is to explore a novel way of producing inhibition of myostatin through oral tolerance therapy with a selective, quantitative blend of amino complex containing fixed amounts of arginine, ornithine, and glycine.
- Maintaining, increasing, and restoring muscle mass in disuse atrophy associated with primary progressive multiple sclerosis (PPMS), weakness and loss of muscle bulk in myopathy, and sarcopenia in normal control subjects will be examined.

BACKGROUND

- Myostatin (MSTN) is a protein from the transforming growth factor-beta (TGF-beta) category whose function, in part, is the maintenance and preservation of muscle bulk and strength.^{1,2}
- Inhibition of the production and activity of MSTN may have therapeutic application in treating muscle-wasting disorders.³
- Regulation of this protein has been difficult, with variable case reports yielding ambiguous results, even with the use of follistatin, a known myostatin antagonist.²⁻³

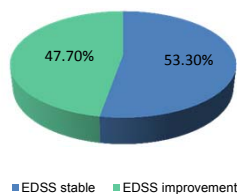
METHODS

- Subjects included PPMS patients affected by disuse atrophy with EDSS scores ≥ 6 (n=15), patients with myopathy (n=8), and healthy control patients ages > 50 years who had experienced some degree of sarcopenia (n=10). They were given a daily oral dose of a selective, quantitative blend of amino complex containing fixed amounts of arginine, ornithine, and glycine.
- The following outcomes measures were obtained at baseline and post-treatment:
 - Serum creatine phosphokinase (CK) and MSTN levels at baseline and monthly for 7 months. MSTN levels were obtained using the Myostatin (MSTN) ELISA kit from antibodies-online.com, which has a sensitivity of 0.28 ng/ml.
 - Dynamometric strength recordings (DSR) for biceps and quadriceps, and muscle mass indices (MMI) at baseline and at 6 months.
 - EDSS for PPMS group at baseline and at 6 months.
- An exercise program was designed and implemented for the patient's functional capacity.

RESULTS

- Baseline demographics:** Disuse atrophy PPMS group had a mean age of 52.3 ± 8.5 years (range 36 to 64 years), 53% female, mean EDSS 6.8 ± 8.5 (range 6.0 to 8.5), mean disease duration 13.3 ± 6.8 years (range 6 to 21 years). Current MS therapy includes natalizumab (N=7), rituximab (N=1), and teriflunomide (N=7). Mean age for myopathy group was 50.0 ± 11.7 years, 62.5% female. Mean age for sarcopenia group was 58.1 ± 5.8 years, 40% female.
- Mean EDSS improvement 6-month post-treatment (Figure 1):** PPMS group had a mean EDSS improvement of -0.5, of which, 7 patients (natalizumab=3, rituximab=1, teriflunomide=3) had an improvement in EDSS score (range -0.5 to -2.0) and 8 patients had stable EDSS score.

Figure 1: EDSS change in PPMS group



- Mean reduction in serum CK and MSTN (Figures 2 & 3):** Compared to baseline, a reduction in CK and MSTN were seen in all 3 groups at 7 months post-treatment.
 - CK:** PPMS -12.6% (p=0.0009), Myopathy -42.8% (p=0.001), Sarcopenia -16.7% (p=0.003)
 - MSTN:** PPMS -41.3% (p=0.0001), Myopathy -32.1% (p=0.0001), Sarcopenia -31.1% (p=0.0001)
- Mean increase in DSR for Biceps and Quadriceps (Figures 4 & 5):** Compared to baseline, an increase in DSR for biceps and quadriceps were seen in all 3 groups at 6 months post-treatment.
 - DSR - Biceps:** PPMS 30.4% (p=0.0001), Myopathy 14.0% (p=0.0006), Sarcopenia 21.4% (p=0.0019)
 - DSR - Quads:** PPMS 47.4% (p=0.0001), Myopathy 17.8% (p=0.0016), Sarcopenia 28.7% (p=0.0001)
- Mean increase in MMI (Figure 6):** Compared to baseline, an increase in MMI were seen for all 3 groups.
 - MMI:** PPMS 16.3% (p=0.0024), Myopathy 9.7% (p=0.0003), Sarcopenia 11.9% (p=0.0001)
- No side effects were reported. Patients tolerated the oral blend of amino complex well.

Figure 2: Serum Creatinine Phosphokinase

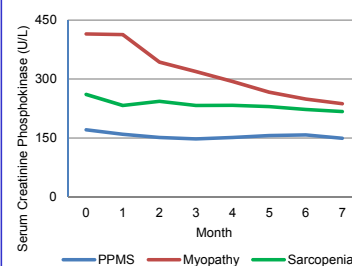


Figure 3: Serum Myostatin

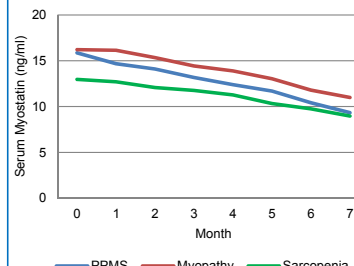


Figure 4: DSR - Biceps

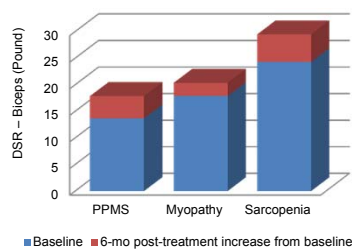


Figure 5: DSR - Quadriceps

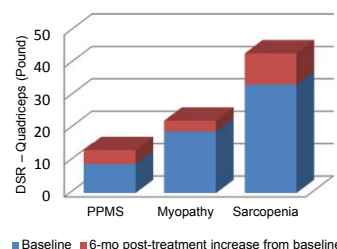
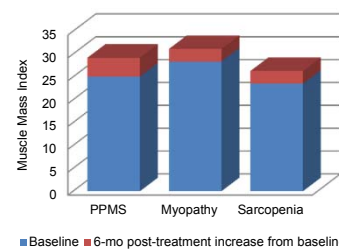


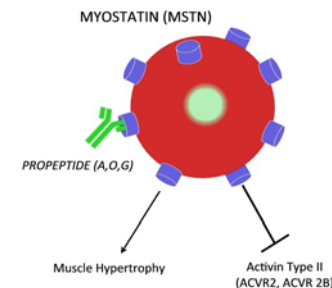
Figure 6: Muscle Mass Index



PROPOSED MECHANISM

- The proposed mechanism of action (Figure 7) is that the peptide sequence of arginine, ornithine, and glycine binds to the MSTN molecule in a non-covalent fashion. This renders the MSTN molecule inert. The effect is only on the MSTN molecule and not on the activin type II receptors.

Figure 7: Proposed Mechanism of Action



CONCLUSION

- Maintenance of muscle strength in neurologic disease is fraught with considerable difficulty and is ordinarily not improved by physical therapy alone.
- Our data suggest that use of a fixed peptide sequence of arginine, ornithine, and glycine may competitively inhibit MSTN.
- The adjunctive use of this form of oral tolerance therapy in clinical practice may prove quite beneficial for patients with PPMS or other muscle-wasting disorders.

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Disclosure:
The authors have nothing to declare