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Treatment of facioscapulohumeral muscular dystrophy with Denosumab

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Summary

Background: Facioscapulohumeral muscular dystrophy (FSHD) is the 3rd most common form of muscular dystrophy. Effective treatments for any of the muscular dystrophies have yet to be realized. This report describes such a treatment.

Case Report: A 66 year old female was diagnosed with osteoporosis. She had been diagnosed with FSHD muscular dystrophy a number of years previously by both genetic and clinical studies. Following a 2 year course with Forteo for osteoporosis, she was given an injection of Denosumab (Prolia) to maintain her bone density. By 24 hours, she exhibited increased strength and a dramatic reduction of her dystrophic symptoms e.g. she could walk unassisted in high heels. She was able to accomplish other things that had not been possible for a number of years. After approximately 5 weeks she gradually lost the newfound strength with a complete loss by about 6 weeks. A second injection of Denosumab resulted in the same effect, i.e. reversal of symptoms and increased functionality. A number of measurements and videos were taken to establish the beneficial effects of Prolia for future studies. This was repeated with a 3rd and 4th injection in order to establish the unequivocal beneficial effects on muscular dystrophy.

Conclusions: Further studies will be required to establish Denosumab as a major "front line" treatment for this disease and possibly other muscular dystrophies.

key words: **facioscapulohumeral muscular dystrophy • FSHD • Denosumab**

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Background

Facioscapulohumeral muscular dystrophy (FSHD) is an autosomal dominant disease and the 3rd most common form of muscular dystrophy [1]. Onset occurs in late teens to early 20s with progressive loss of function. Treatments for the many types of dystrophies remain elusive. A number of "new" and exciting approaches are being evaluated [2]. These include: (a) replacement of the missing protein, (b) stem cell therapy using cells which have the potential to develop into multiple cell types, (c) gene insertion using genes which can manufacture missing proteins, and (d) manipulation of DNA reading frames using antisense oligonucleotides, which are short strands of nucleic acid that target specific genetic instructions such as exon skipping. These approaches hold out hope for real breakthroughs in the future. The present investigators reported previously [3] that diltiazem caused a reduction of symptoms of facioscapulohumeral (FSHD) muscular dystrophy with a concomitant increase in energy suggesting a possible role for calcium misregulation in this disease. Recent observations have noted another potential treatment for this disease which also causes a major reversal of symptoms.

Case Report

One 66 year old female FSHD patient, who has been on diltiazem therapy for decades, and has had a number of spinal surgeries resulting from an automobile accident, was diagnosed with osteoporosis. After being on Forteo for 2 years she was put on Denosumab. A number of changes were noted, which appeared to reverse many of her FSH symptoms. Within 24 hours she was able to walk without a cane, bury her eyelashes, open bottles which she was unable to do prior to the injection, swallow easier, and was physically stronger with far better balance.

Between 6 to 7 weeks after the initial injection she noted a reversal of the beneficial effects and a return of dystrophic symptoms. Because of the major beneficial response following the initial injection, as well as the return of symptoms, a second injection was administered to document the reversal of symptoms. Sixty three days after the first injection a second was administered. Once again, within 24 hours, there was a dramatic reversal of symptoms. The patient was able to whistle, snap her fingers, walk in high heels, play the piano without fatigue, and do many of the things that she has not been able to do for years. In an attempt to document these changes, before the second injection a series of measurements were made by a physical therapist which included grip tests for both right and left hands. Measurements were taken in both sitting, and standing positions, and arms in both straight, and bent in 90 degree positions. A total of three measurements were taken and the strongest recorded. In addition, "sit to stand" tests were done which measured the number of stands a person performs without their hands for 30 seconds. Also, a timed "get up and go" test was performed from sitting to standing then walking 10 feet and returning to a seated position. These measurements were taken prior to and 24 hours *after* the 2nd and 3rd injections, and at approximately weekly intervals. Data shown in Tables 1 and 2 illustrate data from both the 2nd and 3rd injections and include grip strength (Table 1) followed by the other functional tests for the same intervals (Table 2). Videos were also taken to document these responses.

Five weeks after the second injection, certain symptoms started to return. By 6 weeks there was a complete reversal. A third injection was administered 46 days after the second injection. Essentially the course of the disease followed the same patterns noted after the first and second injection i.e. complete reversal of the dystrophic symptoms.

Discussion

It appears that the beneficial effects noted lasted approximately 6 weeks. Considering the half life of IgG antibody, which is approximately 21 days, there would be

Table 2. Mobility Test Prior to and 24 hours after Denosumab.

	Get Up and Go Test* (sec.)	Sit to stand**
Prior	11.0	6.0
24 hrs	6.0	15.0
Prior	27.0	9.5
24 hrs	5.0	18.0

* From seated position, walk 10 feet and return to seated position. Values Expressed are in seconds; ** Number of "sits to stand" in 30 seconds.

Table 1. Grip meter test before and after Denosumab.

	Right hand (lbs. sq. in.)			Left hand (lbs. sq. in.)		
	Mean	SD	Sig.	Mean	SD	Sig.
Prior	45.0	±3.65		45.0	±3.5	
24 hours	54.8	±3.85	≤0.005	49.3	±1.0	≤0.05
Prior	39.8	±5.1		35.3	±3.7	
24 hours	53.2	±2.1	≤0.001	56.3	±1.5	≤0.001

Each mean represents selection of the highest values of 3 tries with the arm held straight and at 90° in both sitting and standing positions. All values for each hand in the above positions were combined and statistically evaluated using a Student's t Test.

approximately 25% of the original antibody remaining at that time. That could be the minimum dose necessary to cause this effect. A fourth injection was administered 41 days after the previous (3rd) injection. A total of 7 injections with 40 to 42 day intervals, were administered with similar results. It is clear that major benefits with concomitant reduction of dystrophic symptoms, were noted with this patient within 24 hours following administration of Denosumab. Maximum benefit usually took several days. Possible explanations for these effects may relate to the ability of Denosumab to prevent binding of the RANK receptor by RankL with the resultant reduction of cytokines, such as TNF which can cause muscle wasting and cellular apoptosis. In addition, possible effects on calcium regulation, which has been reported to be altered in certain dystrophies [4,5] may also be a major factor. In our previous report [3] utilizing diltiazem, which was administered 3 to 4 times daily, effects were limited, and did not result in the remarkable changes noted with Denosumab. The patient is continuing her diltiazem and is on a 41 day schedule for further injections.

CONCLUSIONS

Further studies will be needed to determine if prolonged use of this substance could result in actual muscle repair. Furthermore, it remains to be seen if continued use of Denosumab will remain an effective treatment for this disease and/or other possible neuromuscular diseases.

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