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HAL Id: hal-02394504
https://hal.archives-ouvertes.fr/hal-02394504
Submitted on 4 Dec 2019

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A phase II/II clinical trial of autologous myoblast transplantation in facioscapulohumeral muscular dystrophy

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Introduction

Facioscapulohumeral muscular dystrophy type 1 (FSHD1) is one of the most frequent adult myopathies (1/20,000), with selective involvement of specific groups of muscles: facial, scapular fixator, anterior foreleg muscles, abdominal and humeral muscles. Vastus lateralis (VI) is usually spared clinically until late stages of the disease, and myoblasts grown from VI have similar behaviour in vivo and in vitro than myoblasts from control patients

- Proposal:
  - Transplantation of autologous myoblast from spared muscle (VI) into an affected muscle as the Tibialis anterior (TA) muscle could locally improve the muscle’s regenerative capacities.

Purpose of the study

Primary endpoints: Safety, feasibility
  - Feasibility of cell preparation
  - Safety of intramuscular injections of cells
  - Clinical and biological tolerance of cell transplantation

Secondary endpoints: Follow-up of muscle strength and resistance to fatigue over 2 years
  - Mechanical testing of strength and resistance to fatigue
  - Surface electromyography, MRI and FDG fixation by PET-Scan

Results of Cell Cultures

- Cell culture feasibility
- Cell viability
- Myoblastic differentiation
- Myogenic differentiation
- Cell growth
- Cell proliferation
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PET-Scan analysis

- 3-1g of VI muscle harvested under local anaesthesia in Nice Hospital and shipped to the Saint Louis Cell Therapy Laboratory in Paris. Within 24h, biopsy minced, digested, cleaned and cells grown in a myogenic supportive medium. Cells settled and expanded on days 8, 13, 17, 20/21. Phenotypic characterisation (DGRO assay), viability, molecular biological control, endodtes assessed according to classical procedures. Methodologies, products and clinical protocol validated by regulatory agencies.

Discussion and Conclusions

Cell productions were feasible but the quality of the initial muscle biopsy is important. Cell administrations were feasible and clinically well tolerated by all patients but one. The control of cell local delivery may be improved by echographic monitoring. Results show slight increases in twitch response and slight decrease in fatigue in the 3rd group. The combination of cell type (myoblasts) and of the modality (dense multisite injections) may have positively affected the TA muscle, BUT: No clinically significant gain of function perceived by FSHD patients, and no significant changes were noted at MRI and PET-Scan. The local FSHD1 degenerated muscle environment may be detrimental to the stability of the fibres or of the cytokines, and muscle regeneration may have been insufficient, too tranitory, aborted or too unstable.

The slight muscle strength increase may not be clinically significant for FSHD patients, but may improve the quality of life of patients with more advanced muscle loss (e.g. DMD patients) in other indications.

Specific inclusion criteria

- Men and women aged 18-65.
- Clinical manifestations of DMFSH confirmed by molecular diagnosis (D4 repeat).
- Lack of clinical deficit in at least one VI muscle (scored by assay score at least 10% extension, MRC ≥ 5), or absence of abductor pollicis brevis (assessed by MRC).
- Motor deficit of at least one anterior leg (scored by assay score at least 2).
- At least 4T MSK and fatty infiltration in at least one TA muscle (assessed by MRI).
- At least 3 of at least 3 patients selected in a sequential fashion.

Clinical parameters

- Information collected repeatedly from early (D0) to late phases (D60).
- Clinical monitoring: overall wellness, heart rate and pressure, fever, cutaneous status, pain, redness, external.
- Biological monitoring: blood sampling, sedentarism, infection (CIP), CK, myoglobinemia, myoglutamin, creatinemia, ions, uricemia, phosphorhemia, transaminases.

Microbiologic tests

- NRM image
- At inclusion, absence of fatty infiltration in one VI (donor muscle) and the presence of abnormal fatty infiltration in one TA recipient muscle is documented without Gd-DTPA.
- Graded semi-quantitative scale: expressing the ratio of fat signal / skeletal muscle signal obtained by NRM imaging using Gd-DTPA contrast agent and T2 parameterization below 1, 1 to 2 months after exploration to evaluate the inflammatory reaction and the evolution of the volume of fatty infiltration (at middle and upper parts of the thigh of the leg).
- PET-Scan analysis

- 13C-acetate uptake [14C]acetate accumulates in tissues as a function of their metabolic activity, especially in brain, myocardium and skeletal muscle samples.
- Measurements have been done at the level of TA upon standardized exercise before injections, then 3 and 6 months later to quantify the volume of metabolically active muscle tissue.

PET-Scan evolution

No significant changes were noted over the follow-up period.

Acknowledgments

The authors wish to thank the patients and their families for their motivation, together with the several collaborators involved in the set up of this study at multiple levels.