O for adipogenic differentiation, Alizarin Red S for osteogenic differentiation, and Safranin O for chondrogenic differentiation. Moreover, surface antigen expression of MSCs was measured by flow cytometry. The treatment of immunosuppressants (dexamethasone only, tacrolimus only, or dexamethasone and tacrolimus combined) did not induce noticeable morphological changes or cell deaths. We also found that MSCs maintained the ability to differentiate into osteoblasts, adipocytes, and chondrocytes under all three immunosuppressive conditions. Furthermore, under all three immunosuppressive conditions, MSCs expressed positive markers for MSC (CD44, CD73, and CD90), while they did not express negative markers for MSC (CD11b, CD14, and CD19). Taken together, the use of immunosuppressants (dexamethasone only, tacrolimus only, or dexamethasone and tacrolimus combined) did not change the characteristics of MSCs. Our results provide supportive evidence for the use of immunosuppressants in MSC clinical trials.

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Mesenchymal Stem/Stromal Cells

CLINICAL-GRADE HUMAN SYNOVIAL FLUID-DERIVED MESENCHYMAL STEM CELLS FOR DEGENERATIVE MENISCUS THERAPY

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Keywords: Personalized treatment, mesenchymal stem cell, clinical trial.

Background & Aim: When meniscal tissue is damaged, there is no gold standard medication and/or surgical treatment that can regenerate the damaged tissue. Currently, although the most effective treatment approach is the surgical method-partial meniscectomy, it provides only symptomatic improvement. The aim of this study is to develop the stem cell treatment protocol in addition/alternative to the surgical method adapt it to the clinical practices, suitable for use in human treatment. For this purpose, all steps of the production process as a Good Manufacturing Practices (GMP)-grade cellular therapy product from the collection of the synovial fluid sample from the patient until the release of the final product; the standard operation procedure of the production was prepared according to the legal regulations.

Methods, Results & Conclusion: Therefore, firstly mesenchymal stem cells were isolated from human synovial fluid by xeno-free enzymatic separation under GMP protocols (ESOGÜ, Clinical Research Ethics Committee approval, 11/04/2019-20). hSF-MSCs were cultured until the third passage. Sterility, serology, quality control and stem cell characterization tests were performed for use in human therapy. The final product release for use in treatment was prepared in accordance with the procedure. hSF-MSCs were characterized according to the minimum standard criteria of the International Society for Cellular Therapy (ISTC) guidelines. In addition, sterility, serology, endotoxin and mycoplasma tests were also negative in accordance with the criteria for release as the final product. Finally, the documentation of all stages of the cell processing and manufacturing process of this cellular therapy product has been completed in accordance with the T.C. Ministry of Health, TITCK "GMP Guideline for Manufactories of Medicinal Products for Human Use" and "Communiqué on the Licensing of Human Tissue and Cell Products and the Centres Carrying Out the Production, Import, Export, Storage and Distribution Activities of These Products". As a result, the production process of stem cell therapy product, which has both regenerative and anti-inflammatory activity in the treatment of meniscal damage and complies with legal and ethical regulations, has been made ready for licensing. Acknowledgements: This study was supported by grants from the Scientific and Technical Research Council of Turkey (TUBITAK 20AG003; 20AG031; 118C538).

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Mesenchymal Stem/Stromal Cells

A PHASE 2 CLINICAL TRIAL OF REPEATED INTRATHECAL TREATMENT WITH AUTOLOGOUS ADIPOSE-DERIVED MSC IN AMYOTROPHIC LATERAL SCLEROSIS

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Keywords: amyotrophic lateral sclerosis, mesenchymal stromal cell, neurodegeneration.

Background & Aim: Mesenchymal stromal cells (MSCs) are being developed as a treatment for amyotrophic lateral sclerosis (ALS) and are hypothesized to exert their effects via growth factor secretion and immunomodulation. Following completion of a Phase 1 dose-escalation safety study, we initiated a multi-site Phase 2 clinical trial to study the safety and efficacy of repeated intrathecal treatment with autologous adipose-derived MSCs in people living with ALS.

Methods, Results & Conclusion: During a 3-month lead-in period subjects undergo a fat biopsy for isolation and expansion of MSCs. In this open-label design, subjects receive up to 4 injections (10-100 x 10^6 MSCs), spaced 3 months apart. The primary statistical analyses for efficacy endpoints will be: 1) average slope of ALSFRS-R progression in the study group will be compared with a cohort of subjects from the PRO-ACT ALS clinical trial database that will be matched for age, gender, and riluzole use (5 PRO-ACT subjects for every study subject), 2) average slope of ALSFRS-R progression in the 3 month lead-in period will be compared to the average slope of ALSFRS-R progression in the 12 month treatment period for study subjects. A Responder Analysis will be employed. Serial blood, cerebrospinal fluid, MRI spine imaging, and clinical phenotyping are collected for each enrolled subject. As of January 2023, enrollment is complete with 75 subjects enrolled (Minnesota: 50, Florida: 19, Arizona: 6). 57 people with ALS have received at least one treatment, and 13 subjects are still receiving treatments. Mean age of subjects is 56.3 with a male predominance. 19% have familial ALS and the mean (range) ALSFRS-R at baseline is 37(19-47). This study proved highly feasible with no significant issues in generating sufficient doses, products meeting release criteria, or delivery of these products to the subjects. Baseline plasma neurofilament light chain levels will be reported. Intrathecal MSC therapy is generally well-tolerated with the most common adverse event being temporary back and leg pain. Our multi-site Phase