Summary Col 6 day - 1ª edition (English)

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On June 6th, a highly anticipated event came to fruition: the 1st virtual edition of COL6 DAY. This event, conceived and executed through the exceptional work of the Collagene VI Italia association, led by its president Giulia Da Re, is truly commendable. We congratulate them on the execution of such a significant event and for the opportunity to participate in this global milestone in the trajectory of research related to Collagen VI myopathies and dystrophies. This virtual event hosted speakers and participants from all over the world, bringing together over 150 attendees across 8 panels with more than 20 papers presented. Representatives from all over Europe, the United Kingdom, Asia, the United States, and Latin America were present. It's considered a new global landmark for awareness and connection among patients, families, and researchers from various scientific fields involved in topics related to COL6 myopathies and their potential treatments, therapies, and implications for the lives of those affected by this condition.

Among the presented works, we saw research on therapeutic applications using stem cells, the development and application of gene therapy for correcting DNA information, epigenetic tools for a new form of therapy, mitochondrial therapy, quantification of collagen levels, and refinement of cellular models for COL6. There were also other works focused on patient management, pathways to diagnosis, the importance of registries and subsequent statistical data of the affected population, and affected muscle models with tissue engineering, among others. This revealed a very interesting plurality, demonstrating diverse possibilities in continuous and clear development within the current research landscape in the field of COL6-associated myopathies.

In the first panel, focusing on Asia, Dr. Nana Takenaka provided more details on her research with induced pluripotent stem cells (iPSCs). Their differentiation potential opens the door for the implantation of MSCs (responsible for COL6 synthesis) generated by iPSCs, allowing for the evaluation of implantation results in mouse models. Among the current results, an alleviation of Ullrich Congenital Muscular Dystrophy (UCMD) characteristics in mice and an improvement in some strength levels have been observed due to the partial re-establishment of COL6 presence in muscle tissue. It was also noted that intraperitoneal injection in newborn UCMD mice leads iPSCs throughout the body (systemic delivery) and restores COL6 in all muscles. The next steps in the research will involve testing this

systemic delivery model in larger animals and developing iPSCs with restored COL6 for specific patients.

In the second panel, Aysylu Murtazina, lead researcher at the Neurogenetics Laboratory of the Moscow Medical Genetics Research Center, presented a comprehensive analysis of various patients with different clinical and genetic characteristics. She showcased the variety of manifestations of Ullrich dystrophy, intermediate cases, and Bethlem myopathy. This plurality demonstrates that COL6-related myopathies are a spectrum of disorders with multiple case-by-case variations, and these specific differences in the severity of clinical manifestations naturally affect the time to diagnosis for each patient. Following the panel presentations, Diana S. Abramova, the primary person responsible for the Russian COL6 patient community, presented very recent research that mapped data from Russian patients. This once again showed the variability of patient characteristics, even for those with similar genotypes, highlighting the importance of registries for understanding clinico-genetic correlations and improving predictive diagnosis in the progression of COL6 patient conditions. The subsequent presentation was led by neurologist Anastasya Monakhova on the management of collagenopathies in the Russian Federation. She emphasized the evaluation of patient motor function over time, with a cohort of 88 patients spanning Ullrich, intermediate, and Bethlem conditions. In this monitoring of function loss progression, patients were separated into three groups based on different strength levels. The conclusion was that higher initial motor capacity predicts better long-term outcomes for patients. Finally, the Russian panel concluded with a presentation by Dr. Sergey Kurbatov, who provided general data on rare diseases, myopathies, and their diagnostic methods across various modalities, such as MRI imaging evaluation, force unit evaluation by electroneuromyography, and genetic evaluation. One focus was that diagnoses of spinal muscular atrophy can, in some cases, mask the COL6A3 gene mutation, giving the impression of a distinct diagnosis from collagenopathies due to some similarities in certain clinical characteristics of the patients.

In the third panel, Dr. Priyanshu Mathur detailed the Indian healthcare system and how it addresses patients with collagenopathies, including the socioeconomic difficulties and barriers to a proper diagnosis, and pathways for participation in clinical trials and global research in the long term. Dr. Goknur Halioglu, representing Turkey, continued the panel by sharing the experience of diagnosing COL6-related myopathies over the past 20 years, and how specific patient cases behaved. She brought details on the importance of a careful multidisciplinary approach to diagnosis and improvements in the healthcare system for early

diagnosis. Subsequently, Dr. Sophelia HS Chan from Hong Kong provided an overview reviewing motor and respiratory development, characteristics in each patient type across different parts of the collagenopathy spectrum. She also presented analyses of whole-body Magnetic Resonance Imaging characteristics and muscle biopsy slide analysis, global prevalence, and a brief summary of therapies under development.

In the fourth panel, representing professionals from Germany, Franziska Haarich presented work on molecular biology and epigenetic tools for COL6 mutations. This is a different approach as it doesn't require genetic editing of the mutation, but rather options that highlight or repress characteristics of gene expression (gene expression regulation) in each individual. The work, which is in an earlier stage, has already shown significant reductions in the expression of the mutated gene copy in a COL6A2 case, and a partial restoration of COL6 secretion. This points in the right direction for the developing treatment, which for now continues to seek improved efficiency and new tests in 3D models. The following presentation, led by Prof. Dr. Jan Kirschner, addressed the importance of collecting clinical and genetic data for patient registries. This allows for faster identification in the medium and long term, enabling specific patients to readily participate in clinical trials of developing treatments. Given the rarity of collagen myopathies, registration is crucial for harmonizing international data. It was highlighted that the EURO-NMD center is preparing to facilitate data collection from centers in other regions of the world outside of Europe. Malte Tiburcy concluded the panel by presenting applications of striated muscle modeling through tissue engineering, which enables a clearer understanding of mechanisms and therapeutic strategies for COL6-related dystrophies.

The fifth panel, opened by Dr. Vittoria Cenni, PhD, representing Italy, presented an analysis of the mechanical response in UCMD-derived tenocytes, demonstrating functional and morphological changes in the primary cilium in these cells and changes in cellular response and remodeling. Dr. Paolo Bonaldo presented results from various research he has conducted over the past decades related to reviewing the effects of COL6 alteration in the human body and its morphological and physiological implications, such as in the autophagy process for "cleaning" muscle cells and mitochondrial alterations. Among what was presented are models in both zebrafish and mice that recreate the COL6 mutation, allowing for the identification of nutraceutical approaches to reactivate autophagy and mitigate the structural and functional effects on affected cells. It was also noted in the zebrafish model a variety of drugs already approved by regulatory bodies (FDA) that have the capacity to

improve muscle function, at least in this animal model. In other words, a path is being traced that looks towards a combined treatment, acting at different parts of the cellular processes to counteract the progression of COL6-related diseases. These processes and models are still under evaluation and development, but with increasingly precise modeling of what occurs in the human body. Another researcher from the same group, Dr. Paolo Bernardi, provided more details on mitochondrial therapy to restore its full function, thereby reducing levels of cell death/muscle apoptosis to normal levels. A new round of clinical trials with the drug Alisporivir is about to begin in 2025, with its first results to be validated in COL6 patients starting in 2026.

Another panel featured representatives from France and Spain, moderated by our Scientific Director of Fundación Noelia, Dr. Eduard Goñalons. It began with a presentation by Dr. Valerie Allamand, who demonstrated the refinement of cellular models for COL6-related dystrophies and their benefits for research and patient diagnosis. Following this panel, Dr. Cecilia Jimenez-Mallebrera provided an overview of gene therapy research, including CRISPR-Cas9, gene silencing, and gene editing, which have already shown success in patient-derived cellular models. New resources for monitoring edited genes in animal models were also achieved, and the impacts of editing at the genetic and morphological level in patients with COL6A1 alterations were shown. The last work of the panel was by Virginia ArAchavala, on the Collablot method, which allows for the visualization of COLVI organization and quantification in cells, serving as a method to aid in analyzing the effectiveness of gene editing therapies and their results in edited cells.

The penultimate panel, representing Belgium and the United Kingdom, was opened by a lecture from Dr. Sara Aguti, who discussed peptide-conjugated antisense oligonucleotide therapy for correcting dominant mutations in affected patients. Another representative from Belgium, Dr. Nicolas Deconink, provided an analysis of genetic modifiers that would indicate the severity and progression of diseases, given that there is still an open question about identical mutations in COL6A1/COL6A2/COL6A3 leading to completely different clinical expressions. One genetic modifier was evaluated, however, it did not prove to be a responsible aggravator of the severity of disease expression; other modifiers will be evaluated. Sam McDonald, responsible for global patient registries, presented general data on the registered population primarily in the United Kingdom and the United States, with statistics on the prevalence of genetic and clinical characteristics of the analyzed group, showing the importance of registration for a clearer global understanding of the affected

patient population. Concluding the panel, Francesco Tedesco MD presented a bit about the in vitro modeling of affected muscle tissue engineering models, and also about gene and cell therapies for editing cellular information and correcting transcribed and translated amino acids.

Finally, the last panel featured representatives from both Mexico and the United States of America. Jillian Wise PhD opened the panel by sharing some of her experience as a mother of an affected patient and about project development in the USA, along with therapies under development. Dr. Gustavo Dziewczapolski continued his presentation by reiterating the importance of patient registration and providing an overview of genetic treatments and their possible vectors, as well as animal and cellular tests for COLVI-related treatments. Concluding the event, speaker Juan Manuel Medina PhD discussed conservative management of each patient's clinical condition, highlighting the continuous and personalized need for physical therapy treatment and also the need for supportive orthoses to slow disease progression.

And so, this important event for the entire global COL6 community came to an end. Whether patients, researchers, doctors, parents, or family members, each topic contributed to building a better future and opening space for increasingly more therapeutic possibilities for each patient.