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Risdiplam is a centrally and peripherally distributed, oral survival of motor neuron 2 (SMN2) pre-mRNA splicing modifier approved by the European Commission for the treatment of patients aged ≥2 months with a clinical diagnosis of Type 1, 2 or 3 SMA or 1–4 copies of SMN2.

RAINBOWFISH (NCT03779334) is an ongoing open-label, single-arm, multicenter study of risdiplam in presymptomatic infants with genetically diagnosed SMA from birth–6 weeks of age (at first dose), regardless of SMN2 copy number. The primary analysis will be conducted at 12 months in infants with two SMN2 copies and compound muscle action potential (CMAP) amplitude ≥1.5mV at baseline.

The primary endpoint is the proportion of infants sitting without support for ≥5 seconds. Secondary endpoints include the development of clinically manifested SMA; survival and permanent ventilation; achievement of motor milestones; motor function; growth measures; nutritional status; CMAP; PK/PD; and safety monitoring

As of the data cut-off (1 July 2021), the median age at first dose was 26.5 days for the first 18 enrolled infants. No serious adverse events were reported in infants treated for up to 22.8 months. Efficacy data from seven infants who reached ≥12 months of treatment showed that most infants reached near maximum scores on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders scale. All 7 infants were alive without permanent ventilation, maintained swallowing and feeding abilities, and had not required hospitalization.

RAINBOWFISH will provide valuable information about outcomes following presymptomatic administration of risdiplam.

Digitalized assessing of muscle endurance in adult SMA patients with a novel supervised clinical protocol

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The availability of disease modifying therapies in Spinal Muscular Atrophy (SMA) has created an urgent need to identify clinically meaningful biomarkers and sensitive outcome measures. With this in mind, implementation of suitable outcome measure by the use of web and IT technology could represent an added value to figure out a remote-based assistance strategy positively impacting on patients and medical centers for a new care delivery mode. Through an integrated and multiparametric approach, including deep phenotyping, converging on a single support cloud-based, GDPR-compliant platform (Health 360, Bando Salute Regione Toscana 2018), several clinical parameters have been collected, along with the use of wearable devices for acquiring motor physiological data during neurological examination and the administration of the novel EnduSMA scale evaluating motor endurance. The wearable devices allow to measure several parameters, including surface electromyographic activity, angles of the limbs with respect to the soul, the position of the head with respect to the back, the speed and acceleration of the movements of the body, speed and acceleration of the limbs during the execution of a motor tasks, thus charactering motor performances of patients. The system has been tested and validated in 10 adult SMA type 3 patients.

Overall, the project proposes an innovative model of an integrated smart management system towards a personalized medicine profiling in SMA, which could potentially be translated to other forms of neuromuscular diseases, which share with SMA the phenotypic complexity and difficulty in defining prognostic factors and outcome measures, with added value of the project of involving IT and smart technologies to facilitate data collection, remote monitoring and reprocessing.

Identification of autonomic cardiovascular dysfunction in adult SMA patients: towards the understanding of multisystem involvement in SMA

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Systemic pathology is emerging in spinal muscular atrophy (SMA) with the advent of new disease-phenotypes due to survival motor neuron protein (SMN)-rescue therapies.

Previous reports of a defective autonomic nervous system (ANS) in preclinical models of SMA and severe-

several immune-related adverse events (ir-AEs), including immune-related myositis (ir-Myositis).

Cancer patients treated with ICIs from Jan-2014 to Jun-2022 at a single-center were included. Patients with ir-Myositis were identified. Clinical, diagnostic, and treatment data were collected.

Among 920 ICI-treated patients, we identified nine (1%) ir-Myositis (mean age: 72.4 ± 6.1 years, 89% males). The median latency from ICI exposure was 6.6 weeks (range: 2-48).

Underlying malignancies included melanoma (55%), non-small-cell lung cancer (33%) and Merkel-cell carcinoma (11%). Six patients (66%) developed concomitant myositis and myasthenia gravis (MG/myositis), while three (33%) had isolated myositis. Clinical manifestations included limb-girdle and bulbar weakness, ophthalmoplegia, and myalgias. All patients developed concomitant non-neurologic ir-AEs. Four patients with MG/myositis developed myocarditis, thus configuring a peculiar overlap syndrome (MG/Myositis/Myocarditis).

CK were elevated (mean: 5932 UI/L, range: 380-21.767). Anti-AchR antibodies were positive in patients with MG/myositis (mean titer: 1.89 nmol/L); three patients with MG/Myositis/Myocarditis also had positive anti-titin antibodies. EMG showed myopathic pattern with pathologic spontaneous activity.

All patients received immunosuppressant treatment (9 steroids, 3 intravenous immunoglobulins) and stopped ICI. Five (56%) patients improved, one (11%) remained stable and three (33%) died; patients who died had MG/Myositis/Myocarditis overlap syndrome.

ir-Myositis is a rare complication of ICIs, occurring in 1% of treated patients, and is often associated with concomitant MG and non-neurologic ir-AEs. Ir-Myositis can be severe, with scarce response to immunosuppressant therapies, and even fatal, in particular when associated with MG and myocarditis.

Functional and pharmacological characterization of a Nav1.4 sodium and a ClC-1 chloride channel mutations segregating with myotonia in an Italian kindred

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Mutations in Nav1.4 sodium channel (SCN4A gene) or in ClC-1 chloride channel (CLCN1 gene) cause non-dystrophic myotonias. Next generation sequencing performed on five relatives with myotonic phenotype identified two segregated mutations: p.K1302R in SCN4A and p.H838P in CLCN1. We performed the functional and pharmacological characterization of mutations to evaluate their contribution to myotonia.

Whole-cell sodium and chloride currents were recorded using patch-clamp technique in HEK293 cells transfected with either K1302R or H838P and compared to their wild-type (WT) counterparts. Mexiletine and lamotrigine were tested on WT and K1302R sodium currents, using a voltage-clamp protocol mimicking a myotonic discharge.

The K1302R and WT sodium currents were very similar. Only the voltage-dependence of K1302R activation was shifted by -3 mV, thereby increasing the likelihood of the channel to open at negative potentials. Mexiletine was slightly more potent in blocking K1302R channels at 50 Hz compared to WT (IC_{50}: 6.5 versus 14.6 μM). Lamotrigine inhibited K1302R and WT currents with similar potencies (IC_{50}: 25.9 versus 22.1 μM). The chloride currents carried by H838P displayed a reduced amplitude (-73 % at -100 mV) and a 25-mV positive shift of activation voltage dependence.

In conclusion, the functional alterations induced by p.K1302R and p.H838P are asymptomatic when the mutations are expressed individually. In patients carrying both mutations, the combination of the Nav1.4 and ClC-1 functional defects is likely responsible for the myotonic phenotype. Both mexiletine and lamotrigine might be useful in myotonic patients carrying the K1302R mutation (Supported by University of Bari "Horizon Europe Seeds").

OCTOBER 22/10/2022: 9.30-11.00

IT engineered "smart-shoes" to digitally assess gait dynamics in FSHD patients

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Facioscapulo-humeral muscular dystrophy is one of the most common myopathies in adult patients and growing evidence suggest a reduce prognostic value of the D4Z4 allele length in determining disease course. As subjects with FSHD can display various degrees of disease severity and clinical phenotypes, the Comprehensive Clinical Evaluation Form (CCEF) was proposed by the Italian Clinical Network for FSHD, defining various Clinical Categories by the combination of different features as face and upper limbs involvement, thus identifying phenotypic subgroups. Clinical trials are finally approaching also for FSHD, addressing the pathomechanisms that have been proposed by far as DNA methylation levels, inflammatory response and DUX4 expression. These advancements prompt the need for deep understanding of the molecular causes of clinical differences among patients and precise phenotyping of different clinical forms, in order to identify novel outcome measures for natural history definition and clinical trials. In this setting we aim at evaluating the sensitivity of biosensors-featured "smart-shoes" assessing various parameters as speed of gait and plantar pressure in FSHD adult patients without clinically detectable involvement of the lower leg (i.e. tibialis anterior muscle) at neurological examination. Results will be compared to healthy, age-matched controls in order to highlight early signs of gait disturbances. Application of wearable devices such as the smart-shoes could not only deliver digitized data on a personalized basis but also apply to a novel model of tele-monitoring of patients in daily life.

Retrospective analysis of muscle biopsy findings in a cohort of patients with facioscapulohumeral dystrophy type 1

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Muscle biopsy does not play a definite role in the diagnostic flowchart and the management of Facioscapulohumeral Muscular Dystrophy (FSHD). Therefore, there are no studies that have systematically carried out a correlation of the phenotype and genotype under the light of histopathological findings.

A standardized analysis of histopathological changes in muscle biopsies of FSHD1 patients

The muscle biopsies of 20 FSHD1 subjects were analyzed. In order to standardize the severity of muscle damage, a score ranged from 0 (normal) to 36 was assigned, taking into account several parameters (fibro-adipose tissue, necrosis, nuclear alterations, etc…). The biopsy score was then correlated with the degree of disability of the subjects through the FSHD clinical score and the clinical category identified by the comprehensive clinical evaluation form (CCEF)

Severe changes are present in one third of patients; there is a linear correlation between biopsy score and FSHD score. Subjects with the classic phenotype have worse biopsy scores than subjects with incomplete or atypical phenotypes. Furthermore, a low frequency of inflammatory signs and mitochondrial and oxidative alterations metabolism was observed.

Our data suggest that muscle biopsy could be an additional tool for stratification of FSHD patients for future clinical trials as well. In particular, using a standardized biopsy score can be considered a valid tool for improving the phenotypic characterization and making it easier to compare patients. Finally, the muscle biopsy data could provide useful information for a better understanding of the pathogenetic mechanisms.

X-linked Emery-Dreifuss muscular dystrophy: a multicenter Italian cohort study

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