EPTRI
European Paediatric Translational Research Infrastructure

EPTRI SCIENTIFIC MEETING

BOOK OF ABSTRACTS

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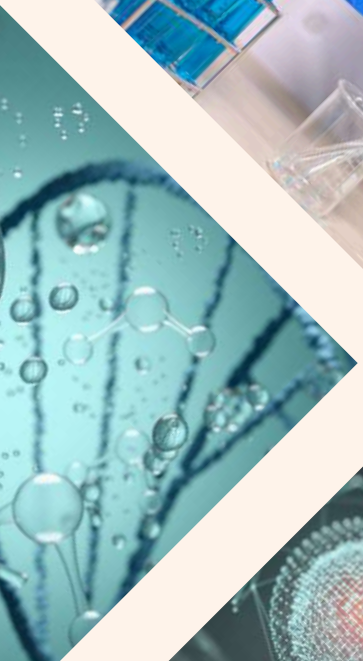

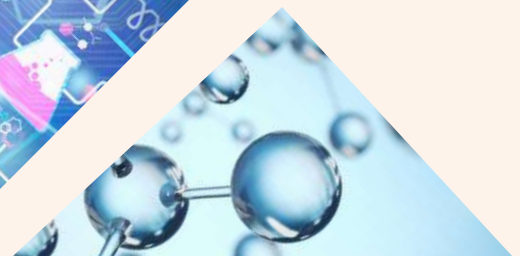

“Advancing Clinical Research in the Paediatric Population”

SPEAKER SECTION

SPEAKER: CLAUDIA PANSIERI

Application of a new methodological approach to overcome paediatric clinical trial challenges: GAPP study

Bayesian adaptive trial design for children from 3 months to less than 18 years of age experiencing moderate to severe chronic neuropathic, nociplastic or mixed pain.

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Gabapentin, although widely used in pediatric patients (3 months to <18 years old) diagnosed with chronic neuropathic, nociplastic or mixed pain in children does not have an approved indication and the efficacy and safety have not yet been well characterized. During the Gabapentin in Paediatric Pain (GAPP) project, funded by the European Commission (GA no. 602962) in 2013, we tried to solve this gap, however, generating evidence based on randomized clinical trials in this population has been extremely challenging due to two main barriers encountered that significantly impacting recruitment potential: a) the required one week wash-out period that was considered not acceptable by many patients/parents, b) the choice of an opioid, as active comparator that still today cannot be considered as a recognised standard of care.

It is in this context that we are currently working to a new GAPP study design aiming to evaluate the efficacy, pharmacokinetics, and safety of gabapentin in paediatric patients with chronic neuropathic, nociplastic and mixed pain, in which, instead of a traditional superiority study we will apply an adaptive study design, and a bayesian methodology, fully in line with the new openings from the European Commission regulations**.** The Bayesian trial design utilizes Bayes theory to generate probabilities based on prior observed data.

This shift to adaptive design should overcome the cited barriers since offers some key benefits:

a) Avoiding the Selection of a Comparator since the adaptive design helps to sidestep this issue by allowing the study to focus on the drug's effectiveness without necessarily comparing it against

a fixed alternative. This flexibility means that decisions can be made during the study, such as modifying dosing, sample size or patient groups based on interim results.

b) Reducing the Sample Size: The Bayesian methodology allows for more flexibility in statistical modeling, which can lead to a reduced number of patients enrolled in the study. This is because Bayesian methods use prior information (like data from previous studies or expert opinion) combined with current study data to draw conclusions, which can achieve sufficient statistical power with fewer participants. The use of the Bayesian adaptive approach in this study design results in the need for a smaller overall number of patients. We computed, for fixed sample size including 32 patients in the naïve cohort, 36 patients in the non-naïve cohort and significance levels $\alpha=0.05$, the power of detecting a positive effect for gabapentin.

c) Reduction of patient burden and increase in ethical compliance: as baseline measurements between two or more treatment groups are not required, there is not the need for a wash-out period. In this way the design enhances ethical compliance, making the trial more patient-centric and reducing risks and discomfort during the trial.

d) Enhancement of patient safety and treatment efficacy: an adaptive design improves patient safety by minimizing unnecessary treatment exposure. Indeed, this approach enables real-time adjustments based on interim analysis of acquired data. It also allows for the early termination of ineffective or unsafe treatments, optimizes dosing, and increases the likelihood that young patients receive therapies with the greatest potential for effectiveness.

A team of dedicated professionals of a no profit research consortium along with six excellence clinical centers with highly skilled investigators across Europe, is currently actively participating in the discussion and is committed to carrying out the new research-driven GAPP study. The goal is to acquire the clinical evidence necessary for obtaining marketing authorization based on the GAPP Paediatric Investigation Plan fulfilment.

SPEAKER: MICHELA STARACE

Paronychia in Selumetinib-treated patients

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In recent years, the management of neurofibromatosis type 1 (NF1), especially for pediatric patients with inoperable plexiform neurofibromas, has been revolutionized using targeted therapies. Selumetinib, a MEK1/2 kinase inhibitor, has been shown to significantly reduce tumor volume, with a positive impact on patients' symptoms and quality of life. However, treatment is often associated with dermatological adverse events that may affect patients' adherence to therapy. Careful preventive and therapeutic management of side effects is key to ensuring the continuity of selumetinib therapy and maximizing its benefits in pediatric patients with NF1.

The most frequent skin reactions include xerosis, acneiform rash, paronychia, periungual pyogenic granulomas, and hair changes such as thinning and pigmentation changes. Xerosis is particularly common in younger children, while acneiform rash and paronychia tend to occur more frequently in adolescents. The latter, appears to show a similar incidence among female and male patients. Mucositis is also a common effect, with an impact on nutrition and the patient's overall well-being. A significant side effect is paronychia with subsequent possible development of periungual pyogenic granulomas, which may cause pain and functional limitations, impairing the patient's daily activities. Clobetasol propionate in occlusion associated with mupurocin, a combination of betamethasone/fusidic acid, and topical beta-blockers represent the main

therapeutic choices for this condition. In severe cases, surgery with chemical matricectomy may be necessary. If these therapies do not show efficacy, dose adjustment or discontinuation of selumetinib may be required.
We conducted a retrospective study, including 23 patients evaluated at our Centre, 8 of whom developed paronychia, arising after the introduction of selumetinib. The clinical and, if applicable, dermoscopic presentation, therapy set and outcome, and any other comorbidities or selumetinib toxicities developed in this cohort of patients were evaluated, as well as the time from the initiation of treatment to the first occurrence of symptoms. A secondary objective is to formulate treatment recommendations that may improve quality of life, during a psychologically and physically demanding course for children and adolescents and enable continuation of ongoing therapy.
To assess paronychia severity, we adopted the MASCC skin toxicity study group's classification, which considers the extent of nail fold involvement, associated symptoms, and required interventions to grade drug-induced paronychia. According to this classification, Grade 1 entails no significant impact on daily activities, including mild findings such as nail fold edema, erythema, or disruption of the cuticle. Grade 2 involves more pronounced inflammation (e.g., edema or erythema with pain), possibly accompanied by discharge or partial nail plate separation. Conversely, Grade 3 indicates severe infection with potential abscess formation or extensive tissue involvement, often necessitating surgical intervention or intravenous antibiotics.

SPEAKER: GIULIO MALTONI

Efficacy of automated Insulin Delivery Systems in children and adolescents with type 1 diabetes: data from a real-world observational study

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Background: Most subjects with Type 1 Diabetes (T1D) do not reach the glucometabolic control targets recommended by the main international societies, expressed as Glycosilate Hemoglobin (HbA1c) and Continuous Glucose Monitoring (CGM) metrics: HbA1c <7% (53 mmol/mol), Time spent In the Range 70-180 mg/dl (TIR) >70%, Time spent Below the Range of 70 mg/dl (TBR) <4% , Time spent Above Range (TAR) >180 mg/dl <25%, TAR >250 mg/dl < 5% and Coefficient of Variations (CV) less than 36%.

The advent of automated insulin delivery systems (AID), although not still fully closed loop systems requiring the intervention of the patient/caregiver for the administration of the prandial bolus, have allowed for improving metabolic control. This is a longitudinal observational study to evaluate the efficacy of AID systems on glycemic control in a population of children and adolescents with T1D in real world.

Patients and Methods: We evaluated HbA1c (the last value and the last 6-month mean value) and CGM metrics of 240 subjects (age 2-18) with T1D (disease duration at least 1 year, on the same treatment for more than 6 months). They were subdivided into 3 groups based on insulin delivery system: Group 1 was AID systems users, Group 2 Sensor Augmented Pump therapy (SAP) users and Group 3 MultiDaily Injections (MDI) + CGM.

Results: Group 1 was composed of 112 subjects (mean age 14,00 +/-2,7 yrs), group 2 27 subjects (mean age 15,1 +/-5,2 yrs) and group 3 101 subjects (mean age 13,7 +/-3,1 yrs). The results are summarized in the table (data expressed as Group: 1 AID; 2 SAP; 3 MDI+CGM, Mean value +/- Std. Deviation)

HbA1c last value % (mmol/mol)	group 1:	6.8*(49) +/-0.7
HbA1c last value % (mmol/mol)	group 2:	7.4 (57) +/-1.0
HbA1c last value % (mmol/mol)	group 3:	7.7 (61) +/-1.1
HbA1c 6 months % (mmol/mol)	group 1:	6.8* (49) +/-0.6
HbA1c 6 months % (mmol/mol)	group 2:	7.5 (58) +/-1.0
HbA1c 6 months % (mmol/mol)	group 3:	7.7 (61) +/-1.3
TIR (%)	group 1:	67.2* +/-12.2
TIR (%)	group 2:	46.3 +/-18.3
TIR (%)	group 3:	50.2 +/-18.8
CV (%)	group 1:	35.7* +/-5.3
CV (%)	group 2:	40.4 +/-11.0
CV (%)	group 3:	38.7 +/-6.1
TAR >180 (%)	group 1:	20.9* +/-6.1
TAR >180 (%)	group 2:	27.8 +/-10.6
TAR >180 (%)	group 3:	27.5 +/-13.1
TAR >250 (%)	group 1:	9.4* +/-8.0
TAR >250 (%)	group 2:	24.0 +/-17.3
TAR >250 (%)	group 3:	21.9 +/-18.3
TBR (%)	group 1:	1.7* +/-1.5
TBR (%)	group 2:	2.7 +/-3.7
TBR (%)	group 3:	3.1 +/-3.4

We found a significant reduction in the mean HbA1c in Group 1 compared to both Group 2 and 3 (p=0,01 and <0,001 respectively). NO difference between group 2 vs 3. As for CGM metrics: the differences between Group 1 vs Group 2 and 3 in TIR, TAR>180, TAR>250 and CV were significant (p<0,001). A significant difference in TBR between Group 1 vs 3, non-difference between Group 1 vs 2.

Discussion and Conclusions: According to the emerging literature, we observed an improved metabolic control with AID systems compared to other insulin treatment strategies with HbA1c mean values in according to the recommended target. Mean values of Time in Range (TIR) increased by 21% and 17% (5 and 4 more hours spent every day in the optimal glycemic range) compared to SAP and MDI treatment respectively, and mean values of Time Above the higher Range of 250 mg/dl (TAR>250) reduced by 15 and 12%, in the absence of significant increases in Time spent in hypoglycemia range (TBR). TAR>180 mg/dl, TBR and CV comply with the international recommendations. In conclusion, AID systems are statistically associated with improved glycemic control compared to other insulin treatment strategies in real life conditions.

SPEAKER: SIFAN HU

Accelerating Safer Administration of Medicines to Children in Low Resource Settings – Bridging Stakeholder Viewpoints.

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*On behalf of European Paediatric Formulation Initiative (EuPFI)

Background: Medication use in paediatric population is prone to dosing error as small dose volumes are required to be administered. Using safe and effective administration devices to prevent over-dosing and under-dosing is a key approach to secure paediatric medication safety. It is especially important to understand the pharmacotherapy needs of children living in resource-limited conditions and find solutions that accelerate the de-velopment and adoption of user-friendly administration devices. Hence, a workshop was held to understand the uptake of the already existing administration devices for oral and respiratory medicines in low- and middle-income countries, and to assess the level of awareness of issues associated with use of administration devices as well as the need of innovative devices.

Method: The workshop featured a panel where researchers shared findings on paediatric medicine administration devices, followed by presentations on clinical and industry challenges. Participants then discussed procedural and operational issues and proposed solutions.

Results: The panel highlighted country-dependent use of devices for paediatric oral and inhaled medicines. Indian HCPs prioritize access, availability, and affordability, while European developers adhere to strict regulations on accuracy, dose markings, and labelling. In India, innovation is limited by lower regulatory reliance, with a focus on simplifying administration. The top-rated solutions, supported by all stakeholders, are device innovation and regulatory harmonization.

Conclusions: Discussions and knowledge shared during this event showed the effectiveness of the workshop in fostering a deeper understanding of the issues regarding use and development of administration devices in low resource settings.

SPEAKER: ROSTYSLAV MARYSHKO

Research and care for children with orphan diseases: experience of Ukraine during the war

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Orphan diseases represent a significant medical and social challenge both globally and in Ukraine. These diseases are characterized by low prevalence and are generally of genetic origin, requiring a

specialized approach to diagnosis and treatment. According to the European Organization for Rare Diseases (EURORDIS), there are approximately 7,000 such diseases worldwide, collectively affecting around 300 million people, which accounts for about 5% of the global population.

In recent decades, there has been a noticeable increase in interest in orphan diseases from both the medical community and the pharmaceutical industry. This is due to several factors. The introduction of innovative genetic and molecular research methods has significantly improved diagnostics, enabling more accurate and timely identification of rare (orphan) diseases.

The adoption of the «Orphan Drug Act» in the United States in 1983 marked a significant breakthrough in scientific research on previously overlooked and underestimated rare diseases. This law has improved the quality of life for patients and stimulated further advancements. Similar legislative measures have also been introduced in the European Union to support the development of medicines for orphan patients. In recent years, leading pharmaceutical companies worldwide have developed a substantial number of treatments, with more than 600 such drugs currently registered.

Ministries of Health Care in many countries are developing national action plans for rare diseases, participating in international initiatives, and sharing experiences to enhance the effectiveness of orphan disease management. Specialized medical institutions or reference centers are being established, where patients can receive comprehensive, highly specialized medical care. Public and private foundations allocate significant funds for research and the development of new diagnostic and treatment methods for orphan diseases. Support for scientific research in this field encourages the development of innovative therapies.

Patient organizations and public initiatives play a crucial role in raising awareness about the challenges faced by individuals with rare diseases. Despite positive developments, many patients continue to encounter difficulties in obtaining timely diagnoses and accessing appropriate treatments. Therefore, ongoing efforts to enhance healthcare systems, support scientific research in diagnostics, and develop accessible therapeutic strategies for those with orphan diseases remain a pressing concern for the global medical community.

Since the onset of the full-scale armed aggression on Ukrainian territory after February 24, 2022, numerous violations of the fundamental rights of children with severe orphan diseases have been observed. These include rights to safety, life, timely medical assistance, health and personal development, personal and family life, inviolability of the home, and state care and protection.

During the full-scale invasion, nearly 70% of Ukrainian children were forced to leave their homes, relocating within the country or abroad. The war has separated children from parents who have joined the defense efforts or were unable to leave Ukraine with their children due to martial law. Children remaining in Ukraine are continually exposed to dangers from mass shelling by Russian forces, damage to energy systems, water supplies, heating infrastructure, destruction of schools and hospitals, and the use of explosive devices against civilians.

The military aggression and escalating threats to children's safety have resulted in many remaining in their permanent residences, residing in temporarily occupied territories, being displaced within Ukraine, evacuated abroad, or relocated to non-government-controlled areas.

One of the most pressing issues under martial law is maintaining and supporting the health of children with orphan diseases who require regular medical supervision. Not all children can receive adequate medical care in their current locations due to ongoing shelling and systematic destruction of critical infrastructure. Parents and children are compelled to seek appropriate medical treatment and rehabilitation abroad.

Ensuring the availability of high-cost pharmaceutical treatments for children with rare (orphan) diseases presents a significant challenge. Currently, it is impossible to obtain accurate information regarding the fulfillment of needs for medications and therapeutic nutrition for these children.

Amid ongoing military actions, Ukraine's healthcare system faces unprecedented challenges. Despite these difficulties, providing medical care to children with rare diseases remains a priority.

Efforts are being made to ensure the continuity of diagnosis, treatment, and rehabilitation even under extreme conditions, as emphasized by the Ministry of Health of Ukraine.

Coordinated efforts by government bodies, the medical community, and public organizations have led to the development of a legislative framework aimed at the prevention and treatment of rare (orphan) diseases. Key regulatory acts include:

1. Law of Ukraine "On Amendments to the Fundamentals of Ukrainian Health Legislation to Ensure the Prevention and Treatment of Rare (Orphan) Diseases" No. 1213-VII, 2014 in which it is stated that a rare (orphan) disease is one that threatens human life or is chronically progressive, leading to reduced life expectancy or disability, with a prevalence of no more than 1:2000 among the population. The state is responsible for organizing appropriate medical care for citizens with orphan diseases, ensuring uninterrupted and free provision of necessary medications and specialized dietary products. To achieve this, a state registry of citizens suffering from such diseases is established.
2. Resolution of the Cabinet of Ministers of Ukraine No. 160 dated March 31, 2015 that approves the procedure for providing citizens with rare diseases with medications and specialized dietary products, defines mechanisms and procedures for delivering necessary assistance to such patients, ensuring continuous and free supply of required treatments.
3. Order of the Ministry of Health of Ukraine No. 778 dated October 27, 2014 that approves the list of rare (orphan) diseases, facilitating standardized approaches to their diagnosis and treatment.
4. Law Adopted by the Parliament of Ukraine in 2021 (Draft Law No. 4662) that regulates state procurement of innovative medicines for treating rare diseases through managed entry agreements that accelerates the process of providing patients with modern and effective medications.

These legislative acts and initiatives have laid the foundation for an effective system of support and treatment for citizens suffering from rare diseases in Ukraine, even amidst ongoing military actions.

Work continues creating a national registry of citizens with rare diseases and integrating it into the electronic health system (eHealth), which will improve the tracking and provision of medical care for such patients.

Despite challenging circumstances, reference and expert centers are being established and maintained, utilizing innovative genetic and molecular diagnostic methods for early disease detection.

Ukraine is actively collaborating with international partners, NGOs, and pharmaceutical companies to ensure the supply of necessary medications and equipment, as well as to exchange experiences in managing patients with orphan diseases.

Given limited resources, standards and clinical guidelines are being reviewed and optimized to ensure maximum treatment and rehabilitation efficiency at minimal cost.

Public organizations play a significant role in organizing assistance for patients with orphan diseases in our country. They actively work to improve the quality of life for patients with rare diseases, providing them with necessary support and resources. These organizations hold conferences, seminars, and events aimed at raising awareness of the issues faced by orphan patients and the need to develop a national strategy for their support.

The Public Union "Orphan Diseases of Ukraine," founded in 2016 through the efforts of approximately 10 public organizations united by the goal of implementing assistance for patients with rare diseases in Ukraine.

In addition to this organization, other public associations in Ukraine support patients with orphan diseases:

1. Charitable Foundation "Orphaned Tits": provides assistance to patients with rare diseases by supplying medical equipment, medications, and specialized nutrition, as well as offering informational and psychological support.

2. Public Organization "Patients of Ukraine": focuses on protecting patients' rights, including those suffering from rare diseases, and promotes improved access to treatment.
3. All-Ukrainian Organization "Joy of Movement": brings together parents facing the challenging chronic childhood disease, juvenile rheumatoid arthritis.
4. All-Ukrainian Association of Disabled Persons with Gaucher Disease: specializes in supporting patients with Gaucher disease by providing information, legal assistance, and facilitating access to necessary treatment.
5. All-Ukrainian Association for Assistance to Patients with Cystic Fibrosis: supports patients with cystic fibrosis by ensuring access to essential medical services and medications.

Efforts to improve medical care for patients with rare (orphan) diseases in Ukraine have yielded positive results. In recent years, there have been notable advancements in the diagnosis and treatment of orphan diseases:

1. Expansion of Neonatal Screening: Since October 2022, Ukraine has implemented an expanded neonatal screening program, testing newborns for 21 hereditary diseases. This initiative enables early detection of rare pathologies and timely initiation of treatment. Regional neonatal screening centers operate in Kyiv, Lviv, Kryvyi Rih, and Kharkiv, facilitating early diagnosis and intervention for rare conditions.
2. Increased Funding: In 2023, the state budget of Ukraine allocated nearly 763 million hryvnias for the procurement of medications to treat orphan diseases, significantly surpassing previous years' figures.
3. Support of Humanitarian Programs: International pharmaceutical companies continue to provide humanitarian aid, supplying patients with essential medications until state funding commences.

The medical infrastructure of Ukraine, providing assistance to patients with orphan diseases, includes specialized centers and programs aimed at early diagnosis, effective treatment, and support for such patients, significantly improving their quality of life. However, the number of such centers remains insufficient, and many patients face difficulties in obtaining the necessary assistance.

In this context, the establishment of reference centers within specialized scientific and practical institutions plays a key role in ensuring quality medical care. These centers help address the shortage of specialized institutions, expanding patients' access to timely diagnosis and modern treatment methods.

As of today, there are 18 such centers operating in Ukraine; however, further expansion of the specialized care network is required to fully meet patient needs.

One such center, established in 2023 at the State Institution "All-Ukrainian Center for Maternity and Childhood of the National Academy of Medical Sciences of Ukraine," is the "Reference Center for Rare (Orphan) Diseases in the areas of systemic, rheumatologic diseases of childhood" (ORPHA 280342).

The Reference Center provides diagnostic and treatment services for children up to 18 years old with rare systemic rheumatologic diseases: juvenile rheumatoid arthritis, systemic lupus erythematosus, juvenile dermatomyositis, and systemic sclerosis.

The center utilizes the resources of a multidisciplinary children's clinic and is one of the few medical institutions addressing orphan rheumatic diseases in Ukraine. A highly specialized multidisciplinary medical team ensures the diagnosis and treatment of the most severe patients from various regions of Ukraine, as well as continuous monitoring of autoimmune process characteristics. The center houses an expert commission for conducting biological therapy for patients with rheumatologic diseases, maintains a patient registry corresponding to the center's profile, and sustains ongoing contacts with patient organizations.

Despite the positive changes achieved in recent years regarding orphan diseases, patients continue to face difficulties accessing timely diagnosis and necessary treatment. The ongoing war has led to a brain drain among medical professionals, complicating the organization of specialized centers.
In conclusion, Ukraine's experience during the war demonstrates the healthcare system's high adaptability and determination in providing assistance to children with rare diseases. Despite significant challenges, government structures, medical institutions, and the international community are working together to improve diagnosis, treatment, and rehabilitation for this vulnerable group of patients.
Efforts must continue to support scientific research, develop modern diagnostic methods, ensure timely detection of orphan diseases, and create and promote medications that will be accessible to patients.
Our experience underscores the importance of prompt response, coordinated actions, and the continuous improvement of medical care standards under extreme conditions. The creation of a national registry and the provision of stable funding for patients with rare diseases remain pressing issues.

POSTER SECTION

Venetoclax and Azacitidine in Pediatric High-risk Myeloproliferative Neoplasms: the AIEOP Experience.

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Background: Refractory and/or relapsed acute myeloid leukemia (AML r/r), advanced myelodysplastic syndromes (MDS-EB), and therapy-related myelodysplastic syndromes/acute myeloid leukemia (t-MDS/AML) represent a significant therapeutic challenge for pediatric hemato-oncologists, as these diseases are often resistant to conventional cytotoxic therapies and have a high relapse rate.
Affected patients have often undergone intensive pretreatment and experienced considerable toxicity, making it crucial to adopt less toxic therapies to minimize further adverse effects.
Aim: In this retrospective, multicenter study, 31 pediatric patients (median age of 10 years, range 2-20) with high-risk myeloid malignancies were treated with a combination of venetoclax and azacitidine (ven-aza) (median number of cycles: 2, range 1-7) at centers affiliated with the Italian Association of Pediatric Hematology and Oncology (AIEOP). The patients were diagnosed with AML r/r (n=18), MDS-EB (n=6), and t-MDS/AML (n=7).
Results: The results showed a complete remission (CR) rate of 48.4%, with an overall response rate (ORR), defined as the sum of CR and PR, of 71%. A total of 58.1% of patients successfully proceeded to hematopoietic stem cell transplantation (HSCT). With a median follow-up of 216 days (32 – 1004)

from the start of ven-aza, the one-year event-free survival (EFS) was 53.5% (95% CI: 35.8%-79.9%), significantly higher in patients who underwent HSCT (p < 0.0001). Ven-aza demonstrated excellent efficacy in the subgroup of patients with AML r/r harboring KMT2A rearrangement and in patients with MDS-EB with UBTF-TD.
Grade ≥3 adverse events included neutropenia (12 patients), febrile neutropenia (8 patients), fungal infections (2 patients), and hypertransaminasemia associated with diarrhea (1 patient). No treatment-related deaths were reported.
Conclusion: Our study demonstrates that ven-aza represents a safe and effective bridging strategy to HSCT in pediatric and young adult patients with high-risk myeloid malignancies.

Preliminary Results of Humoral Response Targeting Specific Epitopes of Human Endogenous Retroviruses in Kawasaki Disease and MIS-C.

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Human endogenous retroviruses (HERVs) are relics of ancestral germline infections by exogenous retroviruses, resulting in proviruses transmitted to offspring and integrated in the DNA. HERVs trigger the expression of inflammatory effectors, like cytokines and inflammatory effectors could, in turn, increase HERVs activation. Aberrant expression of two different families of HERVs (i.e. HERV-W and HERV-K) in blood of KD and MIS -C patients vs healthy controls has been demonstrated. The immune response against HERVs in MIS-C and KD have not previously been evaluated.
Objectives: To evaluate the prevalence and magnitude of the immune humoral response against HERV-W and HERV-K epitopes and interferon regulatory factor 5 (IRF5) in patients with KD and MIS-C. To determine associations of clinical features, presentation, laboratory values and coronary involvement (CALs) with humoral response to HERVs and IRF5.
Methods: Study period: October 2020 to June 2021. Population: contemporaneous KD, MIS-C and COVID-19 patients from 2 sites. KD defined by AHA guidelines and MIS-C by CDC criteria. Demographic, laboratory and echocardiograpic data were performed to all KD and MIS-C patients. The reactivity (IgG) against envelope epitopes of HERV-H, HERV-K, HERV-W and IRF5 was tested by indirect ELISA and mesured as Ab optical density (OD) in patients serum blood samples before treatment and compared to healthy controls (HCs). Correlations between clinical and lab data AND Ab against HERVs and IRF5 were investigated. The study was approved by IRB.
Results: 8 KD, 16 MIS-C and 7 COVID-19 (COV) patients and 41 age- and sex-matched healthy controls (HC) were enrolled. Ab anti Hervs W were significantly different in KD vs COVID (p=0.43) and KD vs HCs (p=0.012), Ab antiHervs H were different KD vs HCs (p=0.008), MIS-C vs HCs (p=0.009), Ab anti Hervs K were different in KD vs HCs (p=0.006) , KD vs HCs (p=0.006), MIS-C vs HCs (p=<0.001), COVID vs HCs (p=0.014), MIS-C vs HCs (p=<0.001) and COVID vs HCs (p=0.014); Ab anti IRF-5 were different among grousps as follows: KD vs COVID (p=0.039), KD vs HCs (p=0.014), MIS-C vs HCs (p=<0.001) and MIS-C vs COVID (p=0.012).
Conclusions: In KD and MIS-C the humoral response targeting specific epitopes of HERVs seems to partially contribute to immune response. We found higher humoral response against HERV-W in KD vs COVID and controls, while lower against HERV-K and IRF5 in controls vs KD and MIS-C. Ab against IRF5 are associated with % of lymphocytes, total days of fever and days before treatment. The elevation of IgG response to HERVs and IRF5 might suggest that exposition to these factors causes a secondary antigenic driven immune response in KD. Larger cohorts are needed to further

investigate the associations with inflammation to shed a light into the pathogenesis of KD, and to define whether they can represent biomarkers for diagnosis and prognosis.

Diagnosis of Iron Deficiency Anemia in Children Using Conjunctival Photography: A Color Intensity Analysis Approach.

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Objective: This study aims to diagnose iron deficiency anemia in prepubescent children by using photographs of their conjunctiva. This method targets diagnosing iron deficiency anemia without the need for blood samples or kits. Early diagnosis aims to prevent problems related to iron deficiency in children and support healthy growth and development processes.
Method: The study included 100 girls and 100 boys aged 3-10 years. High-resolution photographs of the conjunctiva were taken using a smartphone or digital camera. These photographs were transferred to the Image J program, and the intensities of the red (R), green (G), and blue (B) color components were analyzed. The obtained color intensity data were compared with ferritin values to create calibration graphs. From the created calibration graphs, when the mean value of the color intensity of the conjunctival photograph of any child whose anemia status is unknown was placed, the ferritin value and thus the anemia status were determined. Statistical significance between control and healthy groups was given using the Student's t-test. Children with multiple medication use and those with diseases other than iron deficiency anemia were not included in the study.
Results: This method provides a sustainable and inexpensive approach to diagnosing iron deficiency anemia. The color intensity analysis of conjunctival photographs yielded results consistent with hemogram data. The study was successful in diagnosing iron deficiency anemia with an accuracy rate of 82.37%. Thus, early diagnosis of iron deficiency anemia was made possible, and the healthy growth and development processes of children were supported.

Modified-Release Hydrocortisone in Congenital Adrenal Hyperplasia: Improving Biochemical Control and Treatment Outcomes.

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Background: Standard glucocorticoid therapy for congenital adrenal hyperplasia (CAH) often fails to adequately control androgen excess, leading to overtreatment with glucocorticoids and numerous adverse events. In Europe, two innovative modified-release hydrocortisone (MRHC) formulations are available: modified-release hydrocortisone tablets and capsules.
Modified-release tablets consist of an immediate-release outer layer and a prolonged-release core, allowing for once-daily dosing. However, this formulation does not replicate the physiological nocturnal cortisol rise, as cortisol levels increase only after the morning dose.
Modified-release capsules (MRHC, Efmody©, formerly Chronocort) provide delayed release and prolonged absorption, mimicking the natural circadian cortisol rhythm. MRHC is taken twice daily—two hours after dinner and one hour before breakfast—resulting in improved morning control of adrenal androgen markers in CAH patients and better disease management. Approved by AIFA (Determination 110/2021) for CAH patients ≥12 years, MRHC lacks clinical data in adolescents aged 12–18.

Objectives: We investigated whether modified-release hydrocortisone (MRHC), which mimics the circadian rhythm of cortisol, could improve disease control and evaluate its effectiveness, safety, and potential adverse effects

Methods: We conducted a 12-month prospective observational study on 18 CAH patients aged ≥12 who switched from conventional therapy to MRHC. Primary outcomes included reducing 17-hydroxyprogesterone (17OHP) levels below 1200 ng/dL, normalizing delta-4-androstenedione levels, reducing total hydrocortisone dose, and comparing adverse events and adrenal crises before and after the therapeutic switch. Secondary outcomes included ACTH, renin, testosterone levels, and metabolic profile parameters (BMI SDS, growth velocity SDS, and blood pressure).

Results: MRHC resulted in improved biochemical control, with a statistically significant morning 17OHP reduction observed after 3 months of MRHC therapy compared to conventional treatment ($p = 0.013$). However, at 6 months, the decrease was not statistically significant ($p = 0.116$). The percentage of patients with controlled 09:00h serum 17OHP (<1200 ng/dL) was 62.5% at 3 months and 45% at 6 months, compared to only 6% with standard therapy. The mean daily hydrocortisone dose was 15.4 mg/day at baseline and 15 mg/day at 6 months. No severe adverse events or adrenal crises were reported during MRHC therapy. Moreover, no laboratory, genetic, or clinical markers have been identified to predict which patients would benefit more from MRHC over standard treatment.

Conclusion: MRHC improved biochemical disease control in most patients, with a slight reduction in steroid dose over time and no severe adverse events or adrenal crises.