

The ITHANET Meeting

TIF 2013

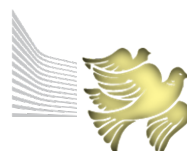
**World Congress
23 October 2013**



Book of Abstracts

ithanet

THALAMBSS



PROGRAM

23 October 2013, 8:30-10:30, CAPITAL SUITE 5

CHAIRS: Marina Kleanthous and Ersi Voskaridou

08:30 - 08:35

Welcoming – Michael Angastiniotis and Marina Kleanthous

08:35 - 08:50

ENERCA – Rare anaemias epidemiology

Michael Angastiniotis; Thalassaemia International Federation

08:50 - 09:05

Increasing access to a safe and definitive cure for severe thalassemia: combining hydroxyurea and aggressive chelation to downstage patients and decrease transplant-associated risk

Lawrence Faulkner; Cure2Children Foundation, Florence, Italy

09:05 - 09:20

ITHANET – Information and database portal for the thalassaemias and other haemoglobinopathies

Petros Kountouris; The Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus

09:20 - 09:35

Promoting data sharing and micro-attributions to refine our knowledge of the epidemiology of α -thalassaemia

Frédéric B. Piel; University of Oxford, Oxford, UK

09:35 - 09:50

Registry for Thalassemia patients: the French experience

Catherine Badens; Reference Center for Thalassemia, Hôpital de la Timone, Marseille, France

09:50 - 10:05

Genotype-phenotype correlation studies for β -thalassaemia patients (THALAMOSS FP7 project)

Marina Kleanthous; The Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus

10:05 - 10:15

IT Infrastructure of the THALAMOSS Project

Petr Holub; Masaryk University, Brno, Czech Republic

10:15 - 10:30

Unraveling the basis of phenotyping heterogeneity in Thalassaemia Intermedia: Prospective applications in genetic counselling and personalized treatment schemes.

Ersi Voskaridou; Laiko General Hospital, Athens, Greece

ENERCA - Rare anaemias epidemiology

Michael Angastiniotis

Thalassaemia International Federation

The difficulty in diagnosing and managing the very rare congenital anaemias, led to the formation by a consortium of experts in Europe, of a Network for Rare and Congenital Anaemias [ENERCA] for the purpose of supporting both medical professionals and patients. The support includes the provision of information, developing guidelines for both diagnosis and guidelines, listing of expert centres and of patient support organisations.

ENERCA has recorded more than 60 rare anaemias and has collected epidemiological information mainly in the European setting. The means used include the creation of registries at both national and European levels, and promoting networking and exchange of expertise among both professional and patient support organisations. Listing of expert centres to which either samples or patients can be referred is also an achievement of the consortium.

The most common of the rare anaemias are the haemoglobin disorders whose epidemiology in Europe, including the effects of migrations, has been documented. Of the other disorders G6PD deficiency and hereditary spherocytosis are relatively common. The current knowledge on the prevalence and incidence of these disorders will be presented.

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Increasing access to a safe and definitive cure for severe thalassaemia: combining hydroxyurea and aggressive chelation to downstage patients and decrease transplant-associated risk

Lawrence Faulkner and Mohamed El Missiry

Cure2Children Foundation, Florence, Italy

Bone marrow transplantation remains the only established definitive cure for severe thalassaemia and can be associated with greater than 90% success rates and improved quality of life. This option however has so far been primarily restricted to a minority of patients with low-risk disease, i.e. no hepatomegaly or organ damage from iron overload.

Current chelation therapy may induce a negative iron balance in patients with thalassaemia and thus decrease transplant-associated risks. Moreover, hydroxyurea (Hu) has been shown to potentially improve transplant results in high risk patients possibly by de-bulking excessive haematopoiesis.

In the preliminary experience of the Cure2Children Foundation thalassaemia cure and prevention projects in developing counties, Hu was combined with continuing chelation therapy as well as reduced transfusion cut off to 7 g/dL with significant reduction in ferritin values. In fact, the safety profile of Hu is well established in both children and adults and may contribute to reduce iron overload by both decreased transfusion requirements and iron absorption. The latter could be mediated by both decrease excessive marrow function including ineffective erythropoiesis and upregulated hepcidin production.

This study proposal aims at exploring the combined use of iron chelation and Hu in patients with severe thalassaemia (inability to keep spontaneous Hb > 7 g/dL), hepato-splenomegaly and high ferritins, particularly if considering the option of bone marrow transplantation. Hu will be used at a starting dose of 20 mg/kg/day adjusted on weekly blood counts to keep the absolute neutrophil count between 500 and 1.000/ μ L and platelet count between 50.000 and 100.000/ μ L. During Hu therapy pre-transfusion haemoglobin threshold will be reduced to 7 g/dL. Weight, height, liver and spleen size on physical exam, any relevant complaint, creatinine, total bilirubin, transaminases and ferritin should be checked monthly. Treatment response will be defined as the ability to maintain a spontaneous haemoglobin above 7 g/dL or reduction of at least 50% of pre-study baseline transfusion requirement (packed red cell ml/kg/month) or any reduction of hepato-splenomegaly or of ferritin by > 50% baseline values for 2 consecutive monthly determinations. If no response is detected after 4 months of appropriate Hu administration the drug will be discontinued.

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ITHANET - Information and database portal for the thalassaemias and other haemoglobinopathies

Petros Kountouris¹, Carsten W. Lederer¹, John Old², Marina Kleanthous¹

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Background and Purpose

Inherited haemoglobin disorders are the most common monogenic diseases. Annually, thousands of newborns bare a serious haemoglobin disorder, with the majority of these births from developing countries. Online resources for the thalassaemias and other haemoglobinopathies are largely divided into specialized sites catering for patients, researchers and clinicians separately. The severity, ubiquity and surprising genetic complexity of the thalassaemias, however, call for an integrated website to pool the expertise of all stakeholders and, in turn, to serve as a free tool to the benefit of patients, scientific and health professionals alike.

Methods & Results

The *ITHANET Portal* (<http://www.ithanet.eu>) represents an expanding resource for clinicians and researchers dealing with haemoglobinopathies and a port of call for patients in search of professional advice. The *ITHANET Portal* integrates information on news, events, clinical trials and thalassaemia-related organizations, research projects and other scientific networks, wiki-based content of protocols, clinical guidelines and educational articles and, most importantly, databases of HbF inducers (*IthaDrugs*) and thalassaemia mutations (*IthaGenes*). The latter is an interactive archive of all sequence variations affecting haemoglobin disorders, including globin loci and disease modifiers, such as BCL11A and KLF1. Apart from the mutations, IthaGenes stores and organizes phenotype, epidemiology, HPLC data, and related publications and external links, while embedding the NCBI sequence viewer in the website for detailed graphical representation of each variation.

Conclusions

As an interactive community tool, the *ITHANET Portal* can serve as a platform for coordination of research projects and invites contributions to its content, including news and events, research and diagnostic protocols, and contact information for clinical, research and diagnostic centers and patient organizations for haemoglobinopathies. Through these contributions and centralized development, the *ITHANET Portal* with its databases has become a comprehensive resource for all information relating to the haemoglobinopathies and is evolving into an indispensable tool for the research, prevention and diagnosis of haemoglobin disorders.

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Promoting data sharing and micro-attributions to refine our knowledge of the epidemiology of α -thalassaemia

Frédéric B. Piel, Bridget S. Penman, Marina Kleanthous, George P. Patrinos, Douglas R. Higgs, David J. Weatherall & Sunetra Gupta

α -thalassaemia is one of the most common monogenic disorders globally. Depending on the degree to which α -globin production is compromised, α -thalassaemia phenotypes range from mild anaemia to lethal *hydrops fetalis*. The most severe clinical complications associated with α -thalassaemia are typically found in Southeast Asia and parts of the Mediterranean region, but α -thalassaemia is also a growing public health concern in other parts of the world (e.g. California) due to migration. Even in countries with a long tradition of screening for the thalassaemias (e.g. Cyprus), our knowledge of the population-level prevalence of α -thalassaemia is extremely patchy. In order to guide public health policies, and answer basic questions about the biology and evolution of α -thalassaemic mutations, it is essential to build a sound epidemiological evidence base. Here, we invite new collaborations to share published and unpublished data relating to the frequency and distribution of α -thalassaemia, so that all existing data can be gathered in a central repository. All unpublished sources will be recognised using the micro-attribution approach previously used for data on the genetic variation of haemoglobinopathies and cystic fibrosis. We intend to launch similar efforts for β -thalassaemia in the future.

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Registry for Thalassemia patients: the French experience

Catherine Badens and Isabelle Thuret

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In France, β -thalassaemia is an extremely rare disease with an incidence of 1 case for 100 000 births. In the context of the French national plan for rare diseases, a National Registry for Thalassemia was created in 2006, in order to collect epidemiological and clinical data, but also data on treatments and clinical investigations. The cases collection is exhaustive and based on crossed information from different sources. To date, 546 patients, 369 Thalassaemia Major and 164 Thalassaemia Intermedia, from more than 80 centers, are included in the registry. Several indicators are monitored such as cardiac MRI use, causes for death, type of iron overload treatments.

This registry has proved to be useful in improving the clinical care of patients by facilitating the incorporation of recent clinical technologies into routine practice. In addition, exhaustive clinical data collection is a valuable tool to evaluate the emergence of new complications related to lifespan increase such as hepato-cellular carcinoma.

Other countries in Europe have developed registries or longitudinal cohort studies for Thalassaemia patients. It could be of interest to establish a common minimum data set consistent with Thalassaemia patients care in order to standardize the studies from one country to another and also to facilitate implementation in countries without registry, providing a generic patient registry template.

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Genotype-phenotype correlation studies for β -thalassaemia patients (THALAMOSS FP7 project)

Marina Kleanthous¹, Carsten W. Lederer¹, Marios Phylactides¹, Petros Kountouris¹, Pavlos Fanis¹ and Roberto Gambari²

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The β -thalassaemias and SCD are severe and rare anaemias with monogenic inheritance, a complex systemic phenotype and treatment-related complications. Novel and mostly experimental treatments, such as the chemical induction of the endogenous β -like γ -globin gene or the restoration of β -globin levels by gene therapy, show great promise but significant variability of success between patients. A small number of modifiers with significant impact on disease penetrance, severity and efficacy of treatments are known, but most remain elusive. Improvements of existing treatments and optimisation and application of novel approaches will critically depend on the characterisation of additional disease modifiers and the stratification of patients for customised therapy.

THALAMOSS (www.thalamoss.eu) is an FP7 project aiming to develop a universal set of markers and techniques for stratification of β -thalassaemia and SCD patients into treatment subgroups for (a) onset and frequencies of blood transfusions, (b) choice of iron chelation, (c) induction of foetal haemoglobin, (d) prospective efficacy of gene therapy. The main research activities of the project include the recruitment of patients and their characterization at the molecular level, omics analyses, new therapeutic approaches and data management and analysis.

For genotype/phenotype correlation studies and patient stratification, detailed clinical data for patients with different genotypes will be collected. Currently more than 1000 patients with 14 different genotypes, as combinations of HbS and four β -thalassaemia mutations common in the Mediterranean region, have been included in the study. In order to expand the genotypic repertoire of the study, we are calling for new collaborators who are eager to have their own patients analysed and subcategorised and who are thus willing to contribute to this study with samples and data.

The expected results from this study are the provision for distinct β -thalassaemia treatment subgroups of novel biomarkers identified by combined genomics, proteomics, transcriptomics and tissue culture assays, as well as the establishment of techniques for the routine detection of these markers and corresponding stratification of patients into treatment groups. In the process, THALAMOSS will also characterise a large number of β -thalassaemia patients at the molecular level and develop new or improved treatments and products for cell isolation.

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IT Infrastructure of the THALAMOSS Project

Petr Holub

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The THALAMOSS project aims to stratify the thalassaemia patients in order to find the optimum treatment for each of the patients. The project will gather significant amount of data including clinical, biochemical and genetic data. The talk will present the data model we have developed for the project, which captures the important semantic relationships in order to allow for automated analysis, as well as first generation of tools for data gathering and distribution inside the project.

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Unraveling the basis of phenotyping heterogeneity in Thalassaemia Intermedia: Prospective applications in genetic counselling and personalized treatment schemes

Ersi Voskaridou

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Growing data in the recent years point into reconsideration of characterization, treatment and genetic counselling of the group of Thalassaemia patients referred to as Thalassaemia Intermedia (TI). Overview of the literature in combination with the data of the Hellenic Reference Centre of Thalassaemia as well as communication with other collaborators, is clearly leading to discuss the re-classification of this group and division into subclasses according to the underlying genotyping, the haematological indices / clinical data and the transfusion dependency.

The current proposal is a necessity, especially as:

1. Genetic counseling of couples at risk to give birth to a TI child is a quite difficult task with elusive information.
2. Personalized medicine is in focus of the patient management worldwide.

Current data reveal that patients with identical underlying mutations of the β -globin gene exhibit a variety of clinical phenotypes ranging from severe cases similar to Thalassaemia Major (TM) to quite mild/asymptomatic ones where practically no treatment is required.

Therefore, as the thalassaemia phenotype can be modified by several factors, many of which have not yet been determined, we propose to establish a consortium of research and clinical groups interested in analyzing the underlying genotypes of the TI patients available, towards unraveling the potential factors /mechanisms acting as modifiers of the disease phenotype. The data collected through the proposed action, evaluated and organized in an open and interactive database (may be through ITHANET portal), are expected to crucially confer to TI genetic counselling and management worldwide.

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