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European Reference Network
for rare or low prevalence complex diseases
Network Eye Diseases (ERN-EYE)

ERN-EYE WORKSHOP ON CLINICAL RESEARCH

21st to 22nd November 2019, Strasbourg, France

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ERN-EYE WORKSHOP ON CLINICAL RESEARCH

ERN-EYE Project Management Team **18/12/2019**

Introduction

Workshop on Clinical Research – November 21st- 22nd, 2019

After two workshops devoted first to ontology, then to genetic testing, ERN-EYE organized a third one on clinical research from 21st to 22nd November in Strasbourg, France. The workshop gathered nearly 100 participants mainly from our member Health Care Providers and the newly designated affiliated partners as well as prestigious guest speakers.

The workshop was opened by Hélène Dollfus, coordinator of ERN-EYE, and Dominique Sturz, European Patient Advocay Group (ePAG) representative from Austria. This workshop was a unique opportunity to exchange on the progress and challenges of the innovative treatments for inherited retinal diseases (IRDs).

The first day of the workshop was dedicated to the state of the art concerning clinical research for IRDs. During the first session, European and international experts presented the very recent settings and results for the current clinical research using gene replacement as well as gene editing approaches.

After an ERN-EYE session dedicated to patient's expectations and realistic outcomes and a round table on current clinical studies and post market in Europe, a satellite meeting was organized by the FHU (Fédération Hospitalo-Universitaire) NeurogenΨcs on the second day. Novel therapies, costs and challenges were discussed and a round table on the interactions between industry representatives and clinicians was the opportunity for all involved professionals to actively participate in the debate. The current situation of retinal implantation was also discussed through a specific round table.

This workshop allowed drawing the clinical research needs in the ERN-EYE member countries, as well as the next issues for ERN-EYE in the coming months on this subject.

ERNs in brief

European Reference Networks (ERNs) are unique and innovative cross-border cooperation platforms between specialists for the diagnosis and treatment of rare or low prevalence complex diseases.

ERNs are virtual networks bringing together healthcare providers across Europe to tackle complex or rare medical conditions that require highly specialized treatment and a concentration of knowledge and resources. They are being set up under the EU Directive on Patients' Rights in Healthcare (2011/24/EU), which also makes it easier for patients to access information on healthcare and thus increase their treatment options.

The ERNs are supported by European cross-border telemedicine tools, and can benefit from a range of EU funding mechanisms such as the "Health Program", the "Connecting Europe Facility" and the EU research program "Horizon 2020".

WELCOME SPEECHES & OBJECTIVES OF THE MEETING

Welcome address – Inaugural welcome speeches

Hélène Dollfus, ERN-EYE coordinator & Dominique Sturz, ePAG representative.

The workshop was opened by Hélène Dollfus, coordinator of ERN-EYE, Dominique Sturz, ePAG representative. Hélène Dollfus was happy to welcome all attendees for this 3rd ERN-EYE workshop, always an excellent opportunity to deeply deal with "hottest" topics for Rare Eye Diseases. Dominique Sturz highlighted the importance of the involvement of patients in the clinical research.

SESSION 1 ADVANCES AND CHALLENGES IN TREATING INHERITED RETINAL DISEASES

(CHAIR: BART LEROY & BIRGIT LORENZ)

Introduction "What are the therapeutic challenges for posterior segment inherited dystrophies?"

Bart Leroy, University Hospital, Ghent, Belgium

Bart Leroy, as an introduction to the workshop gave an overview of the challenges and the needs front of the very exiting progresses in treating inherited retinal diseases observed these last years. Give the correct diagnostic with access to efficient molecular testing (in each country), develop new molecular tools and efficient protocols to use them and to monitor their effect, are key points that have to be definitively addressed in the next few years.

Leber's congenital amaurosis and phenotypic variability and biomarkers: Who and when to treat?

Birgit Lorenz, Justus-Liebig-University, Giessen, Germany

Birgit Lorenz presented the Leber congenital amaurosis. She spoke about phenotypic variability, IRD survey, genotype-phenotype correlation, biomarkers and patient selection. She relied on the fact that genotype-phenotype correlation is a prerequisite for gene therapy, that great advances have been made to document the natural disease course and to show therapeutic effects that are relevant to patients. She concludes on requirements especially viable photoreceptor and RPE cells.

Gene Therapy for Inherited Retinal Dystrophies: Current and future State of Affairs including the long term follow up in the post market era in the USA

Tomas Aleman, Scheie Eye Institute, Philadelphia, USA

Tomas Aleman talked about gene therapy for IRDs and presented an inventory of current and future gene therapy trials in the USA. There are more than 30 trial sites and about 1167 enrolled patients. For subretinal & intravitreal delivery, the majority of studies use Adeno Associated Virus (AAV). The first approved retinal gene therapy, Luxturna, is currently administered at 13 Centers of Excellence:

- 10 Centers in the USA
- 2 Centers in Europe
- 1 Center in Israel

The Oxford experience with gene therapy; paving the way to bring gene therapy for X-Linked Retinal Dystrophies

Susan Downes, John Radcliffe Hospital, Oxford, UK

Susan Downes spoke about Choroideremia characteristics and presented the key elements to establish a gene therapy to treat it. This genetic disorder of sight has a distinct phenotype and an early diagnosis is possible with a good therapeutic window. Susan Downes showed several promising ongoing clinical trials.

CRISPR/Cas-9 Technology for inherited retinal dystrophies

Eric Pierce, Harvard University, Boston, USA

Eric Pierce described the CRISPR/Cas9 technology that mediates genome modification and that has great potential to be used for the treatment of IRDs. Clinical trials using this approach will be starting soon.

Eric Pierce highlighted that gene and genetic therapy approaches need to be developed for all of the genetic forms of IRD and hearing loss and are highly awaited by the patients.

The eco-system of innovative therapies

Florence Allouche, Professeur associé Université Paris Descartes, Paris, France

Florence Allouche spoke about the process of innovation and how academic laboratories and clinicians can be involved in this process. She described all steps of innovation, how to protect our knowledge, how to valorise our know-how and our expertise. She also explained how to connect with the industrial world to valorised inventions (development processes, funding networks…).

SESSION 2: ERN WORKING SESSION – ERN MEMBER STATE SITUATION FOR CLINICAL TRIALS

(CHAIR: HÉLÈNE DOLLFUS & DOMINIQUE STURZ)

Situation of each member state for ERN-EYE

Caroline van Cauwenberg (Belgium, Petra Liskova (Czech Republic), Line Kessel (Denmark), Kristel Harak (Estonia), Saddek Mohand-Saïd (France), Katharina Stingl (Germany), Andrea Sodi (Italy), David Keegan (Ireland), Sandra Valeina (Latvia), Arvydas Gelzinis (Lithuania), Carel Hoyng (Netherlands), Katarzyna Nowomiejska (Poland), João Pedro Marques (Portugal), Kamron Khan (UK), Francis Munier (Switzerland)

All ERN-EYE member countries (plus Switzerland) presented the state of the situation of their country for clinical trials. It allowed to see the differences between the member states and confirmed the need to work together as a network.

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EVI.CRNet role in clinical trials in Europe

Cecilia Martinho, EVICR.net, Coimbra, Portugal

Cecilia Martinho is CEO of EVICR.net that is a dedicated Ophthalmology Clinical Research Network which can provide the overall planning and management needed for members to develop and implement multinational investigator initiated clinical studies. It supports the overall planning and management needed for developing and implementing multinational investigator initiated clinical studies.

SESSION 3: ROUND TABLE

(PART 1, CHAIR: EBERHART ZRENNER & ISABELLE AUDO)

CHALLENGES AND STATE OF THE ART OF CURRENT CLINICAL STUDIES IN EUROPE (PRE MARKET)

QR-110 for CEP290-related LCA

Bart Leroy, University Hospital, Ghent, Belgium

After a brief description of the Leber Congenital Amaurosis (LCA) related to specific mutations in the CEP290 gene, Bart Leroy presented an ongoing clinical study based on a drug developed by ProQR named Sepofarsen (QR-110). This new RNA therapy has been developed for patients with LCA10 due to the p.Cys998X mutation in the CEP290 gene. The results of the phase I/II study were presented and showed that the different dose levels of sepofarsen were safe and tolerated. A phase II/III trial is ongoing to go further.

QR-421a for USH2A-related Retinal Dystrophies & Lentivirus-based Treatments inherited retinal dystrophies

Isabelle Audo, Institut de la Vision, Paris, France

Isabelle Audo mentioned the objectives of the SAR422459 and SAR421869 studies that were done to assess safety and observe for signs of biological activity. The safety profile to date for both gene therapy products reveals no unmanageable safety concern and long term follow-up data are under analysis.

X-linded RP and achromatopsia trials - MEH UK

Michel Michaelides, Moorfields Eye Hospital, London, UK

Michel Michaelides gave a brief overview of Achromatopsia and the RPGR-associated X-linked Retinitis Pigmentosa and presented the trials developed in the Moorfields Eye Hospital. Thus, 6 phase I/II trials based on AAV-CNGA3 gene therapy were developed with AGTC, Tubingen University Hospital and MeiraGTX and 3 phase I/II trials based on AAV-RPGR gene therapy were developed with Biogen, MeiraGTX and AGTC. All gene therapy trials are ongoing.

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Usher syndrome trials

Francesca Simonelli, Università degli Studi della Campania, Naples, Italy

Francesca Simonelli presented the Usher syndrome trials. A trial exists in a phase I/II open label, dose escalation, safety study in subjects with Usher syndrome type 1B (USH1B), using the mixture of two AAV vectors to deliver the gene for human MYO7A. The objectives are to do preclinical studies, aiming to develop clinical grade vector and clinical studies.

Achromatopsia

Susanne Kohl, University of Tübingen, Tübingen , Germany

Susanne Kohl presented the first gene therapy trial in Germany about CNGA3-associated Achromatopsia. There is currently a genetic data of ~1,440 patients from 1,060 families. The first patient has been injected in 2015. 9 patients are participating in the trial: 8 males, 1 female (24 - 59 years of age at enrolment). 9/9 surgeries were completed successfully with full anticipated dose delivered

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SESSION 4 : PATIENT'S EXPECTATIONS AND REALISTIC OUTCOMES (CHAIR : RUSSELL WHEELER AND DAVID KEEGAN)

What are the patients' and parents' perspectives?

Christina Fasser, Retina International, Zurich, Switzerland

For the patients, the main objectives are to get treatments, get them to the patients, get research to find treatments for all and get young clinicians interested and trained.

The new challenge is to include the patients at each stage, hand to hand with clinicians: inclusion in the clinical trials, diagnosis, treatments, etc.

Patient reported outcomes in visual research

Orla Galvin, Retina International, Dublin, Ireland

Orla Gavin highlighted the extreme importance of patient's voice. As a patient organisation, Retina International represents them and act to promote the incorporation of a patient centered approach. Patient's involvement ensure that the priorities of researchers, clinicians, funders and policymakers are aligned to the needs and priorities of those who experience retinal degeneration – the patients, and those who care for them – the clinicians.

Image based outcomes in retinal trial: how reliable?

Philipp Herrmann, University Hospital, Bonn, Germany

Philipp Herrmann spoke about image based outcomes in retinal trials. He explained that imaging based outcome measures are objective and robust. Artificial Intelligence prediction models of retinal function may be useful to monitor disease progression and could be used as outcome measure in investigational trials. New approaches allow further insight in disease pathogenesis and have potential as adequate trial endpoints.

Pediatric specificities in trials

Elise Héon, Hospital for Sick Children, Toronto, Canada

Elise Héon mentioned the specificities for children in the clinical trials. For her, it is important to remember that children are not little adults.

Their specific needs and abilities must be considered in trial studies. IRDs are early onset and trial design should be adapted to include children. She presented useful examples for clinicians.

Morphological & Functional Outcome Measures

Hendrik Scholl, Institute of Molecular and Clinical Ophthalmology Basel (IOB) & Department of Ophthalmology, University of Basel, Switzerland

Hendrik Scholl presented the ProgStar Study that aims to determine the best outcome measurers to accelerate evaluation of emerging treatment and to better understand the progression of the Stargardt disease. He highlighted that visual acuity has limited value as primary endpoint for interventions that aim to slow disease progression, that the lesion growth measured by fundus autofluorescence could be established as a primary outcome measure for clinical trials in Stargardt disease, that microperimetry allows to detect loss of retina light sensitivity and that structure function correlation is possible and will allow to support structural endpoints.

SESSION 5: ROUND TABLE (Part 2)
Challenges of current clinical studies and post market in Europe: state of the art – where are we?

(CHAIR: EBERHART ZRENNER AND ISABELLE AUDO)

How to set up a gene therapy unit & participate in phase IV patient registries?

Eberhart Zrenner, University Eye Hospital, Tübingen, Germany

Eberhart Zrenner gave an overview of the ideal setup of a gene therapy unit. He show that an interdisciplinary interaction of geneticists, IRD specialists, a pharmacy team, trained surgeons, technical staff dedicated to trials and also an administrative expert team including adviser on regulatory is a key point to organise an efficient therapy unit. He also presented a setup of an observational, muti-center, post-approval registry design to collect data on long-term safety outcomes in patients treated with Luxturna.

LUXTURNA the XV-XX experience; getting on the market

Saddek Mohand Said, CHNO des Quinze-Vingts, Paris, France

Saddek Mohand-Saïd presented the experience of the XV-XX hospital with Luxturna. There are 12 patients treated (both eyes each). To date, the obtained results are consistent with the clinical trial data. There was an improvement of patient performances in mobility testing, and retinal sensitivity (FST) but a limited VA and VF improvement.

All patients reported positive subjective appreciations:

- Improvement of vision in dim light conditions. («everything seems brighter »)
- Reduced difficulties to move
- Gaving up the use of certain technical aides (headlamp,…)
- Noticeable change in visual behaviour noted by the parents and school educators in both patients

Leber Hereditary Optic Neuropathy - Clinical Challenges and Therapeutic strategies

Patrick Yu Wai Man, University of Cambridge, Cambridge and Moorfields Eye Hospital, London, UK

Patrick Yu Wai Man presented Leber Hereditary Optic Neuropathy (LHON), an important cause of mitochondrial blindness among young adults. LHON research is entering an exciting translational phase.

He advises to give hope to the patient – but also be frank about the current (limited) treatment options.

Patient recruitment and clinical trial design need careful (and early) consideration appreciation.

LHON gene therapy advances & challenges

José-Alain Sahel, Institut de la Vision, Paris, France

José-Alain Sahel presented a gene therapy (GS10) to treat LHON developed in collaboration with GenSight Biologics and based on the mitochondrial targeting sequence technology to shuttle mRNA directly to affected mitochondria. He briefly showed the development of the study started in 2011 from the proof of concept in animal, to the ongoing phase III bilateral study. To date, all the results are conclusive and promising. He also presented a local biodistribution study in non-human primates, to observe the transfer of DNA from the injected eye to the contralateral eye. This observation must be taken into account for future developments or to an unbiased results analysis.

Friday afternoon: ERN-EYE joint satellite meeting organized by FHU Neurogenycs