Delivering on the promise: the clinical application of new diagnoses and treatments for RD

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PERSPECTIVE/ DISCLAIMERS

• Doctor with >24 years experience in NMD
• Co-ordinator of TREAT-NMD (EU FP6 Network of Excellence)
• PI on several clinical trials in Duchenne muscular dystrophy
• Advisor to AVI, PTC, Summit, Prosensa/ GSK, Lilly, Pfizer on clinical trial design for NMD
• Vice Chair of EUCERD and EUCERD Joint Action co-ordinator
• RD Connect WP leader: Impact
LECTURE OUTLINE

• Using DMD as a case study: how research and infrastructure are both essential to develop new therapies
• Delivery of diagnostics and therapies will rely on (EU) strategies to deliver holistic rare disease services
• Access to new drugs: tensions and synergies between research and service delivery
1 in 5000 male births

Progressive and incurable

Steroids: +4 years ambulation

Cardiac meds: Prevent/treat cardiomyopathy

Ventilation: +> 9 years added survival

DUCHENNE MUSCULAR DYSTROPHY

THE CURRENT PRADIGM OF CARE
MOLECULAR CHARACTERISATION AND APPROACHES TO THERAPY

- Dystrophin gene identified 1986
- Mutation analysis widely available
- Animal model (mdx) extensively studied
- 2013.... 42 open clinical studies (March)
THE TRANSLATIONAL PATHWAY:
“THIS GENE DISCOVERY OPENS THE PATH TO THERAPY……”

Gene identification/pathophysiology
- Biomarkers
- Animal models
- Delivery mechanisms
- Proof of principle studies

Trials
- Diagnosis/care standards
- Natural history
- Patient Registries
- Trial sites
- Outcome measures

Therapy delivery
- Regulatory affairs
- Ethics
- Commissioning/health economics
EXPERIMENTAL THERAPIES FOR DMD - THEMES ENTERING THE CLINICAL ARENA

- Upregulation of alternative proteins
- Increase in muscle bulk
- Addressing downstream pathology with novel or repurposed drugs
- Gene transfer
- Cell therapies
- Modification of the mutation
  - Exon skipping
  - Stop codon suppression
PAST EU INVESTMENT IN NMD INFRASTRUCTURE

• TREAT-NMD (FP6 Network of Excellence)
• CARE NMD (Health Programme funding)
• BIO-NMD (FP7)
• NMD-Chip (FP7)
• Key patient organisation funding and involvement
• Major international collaborative effort

FACILITATED DEVELOPMENT OF TRIAL READINESS IN NMD THROUGH THE GENERATION OF TOOLS AND RESOURCES
# UTILISATION OF TOOLS

**Collaborations include:**

- Acceleron
- AVI Biopharma/ Sarepta
- Biomarin
- Debiopharm
- Genzyme
- Prosensa/ GSK
- PTC Therapeutics
- Santhera
- Trophos
- Academic studies (NIH, AFM, Jain Foundation....)

**Activities include:**

- Preclinical and biochemical OM consensus
- Patient and trial site enquiries
- Patient recruitment
- SAB meetings
- OM selection and training
- CRO support
- Preparing funding applications
- TACT appraisal
"PRECISION MEDICINE" FOR DMD: TARGETING NONSENSE MUTATIONS

- PTC124 (ataluren) targets nonsense mutations (13% DMD)
- Phase 2b study completed (140 patients)
- Phase 3 study initiating soon
- EMA currently considering conditional approval
“PRECISION MEDICINE” FOR DMD: ANTISENSE OLIGONUCLEOTIDES:

- Two technologies, two sets of trials targeting exon 51 skipping
- Applicable to around 17% patients
- Several complete and ongoing studies
- FDA approached for expedited approval (Sarepta)
- GSK/Prosensa preliminary data entering public domain
Numbers on lines are ages of boys in years at Week 141.
DMD: LESSONS LEARNT

- Gene identified 1986: two drugs seeking conditional approval 2013: efficacy questions remain
- Pharma has actively engaged
- Infrastructure development has supported the progress of promising molecules into trials
  - Eg global patient and trial site registries
  - TACT appraisals
- Involvement of patient organisations at all stages has driven the process

WHAT NEXT?
WHAT NEXT?

- Sustainability of tools and resources for future trials and delivery of therapeutics
- Development of next generations of drugs
  - Increasingly rare patient groups
- Access to drugs?
  - National variation in commissioning/reimbursement

LESSONS FOR THE WHOLE RD FIELD
THERAPY DELIVERY: ACCESS AND SUSTAINABILITY

- Gene identification/pathophysiology
  - Biomarkers
  - Animal models
  - Delivery mechanisms
  - Proof of principle studies

- Trials
  - Diagnosis/care standards
  - Natural history
  - Patient Registries
  - Trial sites
  - Outcome measures

- Therapy delivery
  - Regulatory affairs
  - Ethics
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Logos:
- IRDiRC
- EUCERD
EU STRATEGIES FOR HOLISTIC DELIVERY OF RD CARE OFFER HUGE OPPORTUNITIES

- Ideals encompassed in Commission Communication and Council Recommendation
- Span the whole pathway from incentives for orphan drug development to delivery of care
- EUCERD set up to support the EC in the delivery of its RD policies
CORE PRINCIPLES RELEVANT TO RD SERVICE AND THERAPY DELIVERY

• National plans for RD to be in place 2013
• National plans should include a commitment to RD research
• Guidance available on centres of expertise and the European Reference Networks which will link CEs
• Patient registries should be established to serve needs of community at national/international level
• All RD patients will have access to care
PLANNING A PATHWAY OF CARE

Policy issues

National plan
- NP delivers CEs, registries
- CEs linked in European Reference networks

Access to MDT via CE
- CEs, ERNs patient registries
- Delivery of care and new therapeutics

Patient impact
PIVOTAL ROLES OF PATIENT REGISTRIES

- Identification of patients for health service purposes
- Identification of patients for research and trials
- Monitoring of care standards, delivery of care
- Natural history studies
- Post marketing surveillance....

Unifying solutions are required in order to address current duplications of effort
**DEVELOPING THERAPIES**

- Access to patients
- Access to experts
- Knowledge of natural history
- Best delivered via expert centres, patient registries and networks

**DELIVERING THERAPIES**

- Critical mass of patients
- Multidisciplinary experts
- Ability to monitor care and impact on NH
- Best delivered via expert centres, patient registries and networks
IN OTHER WORDS......

• If we can get the kinds of centres of expertise and European reference networks which have been recommended by EUCERD with the underpinning of comprehensive patient registries, the future of RD therapy development and ultimate delivery will be in safe hands
THE RISKS OF NOT DOING IT

• More of the same
  • Two tier healthcare for RD patients
  • Fragmentation of scarce resources
  • “Hidden” costs of doing nothing will continue to be borne by affected people and their families
TENSIONS

- Competition for scarce resources
- Sustainability of research infrastructures
- Limits of the service structures proposed and developed
  - Applications of future cross border healthcare provision
ADDITIONAL VARIABLES

- Big pharma attention span
- Regulatory issues
- Commissioning and reimbursement debates
- National variations in access to approved drugs and compassionate use

Need for “MOCA”
OPPORTUNITIES TO DELIVER

• With excellent science and pharma engagement RD therapies should be developed faster
  • We need to be ready!
• An equal emphasis needs to be put on regulatory and commissioning structures to ensure good science leads to access to trials and ultimately effective drugs across national boundaries
• Services need to be systematically embedded within national and international systems for sustainable delivery of research, development and care
THANKS!