HOW TO BUILD A REFERENCE CENTER

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Mario Negri Institute for Pharmacological Research

June 16 – 19, 2016
Amsterdam, Netherlands
CASE REPORT

- On August 15, 1988 B.L, a 21-year-old-man was admitted to the Unit of Nephrology of Bergamo Hospital because of:
  - fever
  - jaundice
  - confusion
  - aphasia
  - migrating paresthesias
  - visual abnormalities

- Laboratory findings
  - Hct: 27%
  - LDH: 2343 I.U./L
  - Platelet count: 27 x 10^3/µl

- Diagnosis: TTP

- Treatment: Plasma exchange

- Outcome: Full recovery of the acute episode
Since August 1988

- Almost 2-hundreds (monthly) recurrences of TTP
- Recovery of acute episodes with plasma therapy
- Progressive renal function deterioration
- Started chronic dialysis (*March 3, 2001*)
- Persistency of monthly recurrences with predominant gastrointestinal symptoms and occasional gastrointestinal bleeding
PLASMA EXCHANGE vs INFUSION IN CHRONIC RELAPSING TTP

Ruggenenti et al., Am J Kidney Dis, 1993
PLASMA INFUSION vs REMOVAL IN FAMILIAL AND RECURRENT TTP

Ruggenenti et al., *Am J Kidney Dis*, 1993
REGIONAL NETWORK FOR RARE DISEASES

2001 → 13 Presidi

2015 → 38 Presidi

- Centro di coordinamento
- ≤ 80
- 81 - 149
- ≥ 150

Number of diseases served by Reference centers
REGIONAL NETWORK FOR RARE DISEASES
EVOLUTION OF REFERENCE CENTERS

N° Reference centers

+ New endprsments - Withdrawal
REGIONAL NETWORK FOR RARE DISEASES

DISEASES THAT ARE LESS RARE HAVE HOWEVER MORE REFERENCE CENTERS

No. Reference centers

- < 0.002%
- Tra 0.002% e 0.004%
- Tra 0.005% e 0.01%
- > 0.01%

Rare Disease Prevalence

KDIGO
Regional Network for Rare Disease Working Group

• Goals
  – The Working Group establishes uniform strategies for the reference centers to pursue prevention, surveillance, diagnosis and treatment of rare diseases

• The Working Group is composed by representatives of
  – Region
  – Reference centers
  – Coordination Center
  – Local health authority
  – Patient associations
February 29, 2008
1st Rare Diseases Day

COORDINATION CENTER: CONSULTING ACTIVITY
COORDINATION CENTER: CONSULTING ACTIVITY

- Pazienti e Familiari
- Operatori Sanitari

Yearly consulting activity from 2002 to 2014.
Regional Networks evolution in Italy

2001

2007
**Patient distribution by age and gender**

- **Lombardy population**: 9,973,397*
- **All RD cases**: 54,647
- **Diseases**: 291
- **Prevalence**: 548/100,000

*ISTAT Italian Population Census – January 1st, 2014
Diagnostic, Therapeutic and Social Care Pathways (PDTA)

Since 2012 the Regional Network has promoted the development, through conferences of experts, of shared pathways for the diagnosis, treatment and social assistance to patients with rare disease.

These pathways are intended to offer the best quality of care whereby optimizing the use of resources:

- **632** health care professionals were involved
- **31** reference centers
- **33** patient associations

- **110** PDTA were prepared

- They cover approximately **72 – 87%** of rare disease recorded in Lombardy
**PDTA are available at the Coordination Website**

* dal 30 marzo 2011
HOW THE REGIONAL NETWORK IS EVALUATED BY THE PATIENTS

1 = per nulla soddisfatto
5 = molto soddisfatto

Assistenza socio-sanitaria globalmente ricevuta
Presidio di riferimento per la malattia
Medico di Medicina Generale o Pediatria di Libera Scelta
Distretto socio-sanitario/Azienda Sanitaria Locale (ASL)
Servizi sociali (del Comune o di soggetti delegati)

"Malattie rare: rilevazione dei bisogni assistenziali e definizione di misure a sostegno". Decreto n. 7771 del 11.09.2012, Direzione Generale Sanità, Regione Lombardia
Éupolis Lombardia, Edizione: aprile 2014
EXPERTISE AND ORGANIZATIONAL SUPPORT FOR CLINICAL STUDIES

EUROPEAN SCHOOL FOR RARE DISEASES

The Center is the site of active cultural activity at several levels, aimed to both specialists and training health professionals.

Regular courses for training in clinical research are addressed to:

- Medical doctors
- Registered nurses
- Statisticians
- Monitors
- Bioengineering
- Epidemiologists
- Informatics
Prevalence: 1,6/1,000,000 persons
CFH 76 mutations

CFB 5 mutations

CFI 23 mutations

C3 12 mutations

MCP 28 mutations

TM 6 mutations

Newcastle
Paris
Toulouse
Bergamo
Madrid

KDIGO
COMPLEMENTS ABNORMALITIES IN 272 PATIENTS

Cumulation incidence (%)

<table>
<thead>
<tr>
<th></th>
<th>CFH</th>
<th>MCP</th>
<th>CFI</th>
<th>C3</th>
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<tbody>
<tr>
<td>1</td>
<td>S</td>
<td>T30Nfs10X</td>
<td>I208Y</td>
<td></td>
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<tr>
<td>2</td>
<td>I</td>
<td>G1194D</td>
<td>F242C</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>I</td>
<td>G1194D</td>
<td>F242C</td>
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<tr>
<td>4</td>
<td>F</td>
<td>R1210C</td>
<td>Y29X</td>
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<td>5</td>
<td>I</td>
<td>R1210C</td>
<td>C35Y and R59X</td>
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</tr>
<tr>
<td>6</td>
<td>I</td>
<td>R1210C</td>
<td>C35Y and R59X</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>S</td>
<td>R1215Q</td>
<td>R103Q</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>F</td>
<td>N767Kfs7X</td>
<td>H183R</td>
<td>I340T</td>
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<tr>
<td>2</td>
<td>S</td>
<td>P968fs947X</td>
<td>E554V</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>I</td>
<td>S1191L</td>
<td>G1094R</td>
<td>R161W</td>
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<tr>
<td>1</td>
<td>I</td>
<td>V1197A</td>
<td></td>
<td></td>
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<tr>
<td>2</td>
<td>F</td>
<td>R341H</td>
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</table>

The patient and the unaffected mother and brother carry a very rare genomic rearrangement between CFH and CFHR1 genes generating heterozygous CFH/CFHR1 hybrid protein in which SCR 1-19 are derived from CFH and SCR 20 from SCR 5 of CFHR1 by non allelic homologous recombination.

Valoti et al., JASN, 2015
LONG-TERM OUTCOMES FOR aHUS PATIENTS

Patients free of events
Death or ESRD (%)

Follow up (years)

CFH mutation

Noris et al., *C J Am Soc Nephrol*, 2010
Combined kidney and liver transplantation for familial haemolytic uraemic syndrome

Giuseppe Remuzzi, Piero Ruggenenti, Daniela Codazzi, Marina Noris, Jessica Caprioli, Giuseppe Locatelli, Bruno Gridelli

Lancet 2002; 359: 1671–72
Rat kidney reperfusion
EFFECTS OF 52 WEEKS OF ECULIZUMAB THERAPY IN PATIENTS WITH PLASMA DEPENDENT OR PLASMA RESISTANT ATYPICAL HUS

<table>
<thead>
<tr>
<th></th>
<th>Dependent (n = 20)</th>
<th>Resistant (n = 17)</th>
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</thead>
<tbody>
<tr>
<td>Persistent remission</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>Need for plasma therapy</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Serious treatment-related adverse events</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

330,000 euro per patient per year
Rare diseases and effective treatments: are we delivering?

Lucio Luzzatto, Carla E M Hollak, Timothy M Cox, Arrigo Schieppati, Christoph Licht, Helena Kääriäinen, Giampaolo Merlini, Franz Schaefer, Steven Simoens, Luca Pani, Silvio Garattini, Giuseppe Remuzzi
Ogni 15 giorni per sempre?
ALTERNATIVE PATHWAY ACTIVATION IS IMPAIRED IN SOLID BUT NOT IN FLUID PHASE

Alternative pathway activation (spontaneous hydrolysis, bacteria, viruses)

Fluid phase C3 convertase

C3

C3b

C3b

C3a

C3b

CFH

CFB

CFI

Bb

iC3b

C5

C5a

C5b-9

C3 convertase

C5 convertase

Surface bound C3 convertase

C3a

Glycosaminoglycans

Endothelial cell
COMPLEMENTing the diagnosis of aHUS

Vahid Afshar-Kharghan  THE UNIVERSITY OF TEXAS MD ANDERSON CANCER CENTER

Normal serum

Resting endothelium

Activated endothelium

Acute aHUS serum

C5b-9

C3b

C5b-9

C5b-9

aHUS serum in remission

Asymptomatic carrier serum

Normal serum

ADP

C3b

C3b

C5b-9

Resting endothelium

Activated endothelium

C5b-9

C5b-9

C5b-9

C5b-9

KDIGO
- Control or aHUS serum
- anti-C5b-9 Ab staining
- Confocal microscopy

HMEC-1 → Static incubation
10 min → 4 hours → C5b-9 deposition

Resting endothelium

Activated endothelium

Noris et al, Blood, 2014
April 2007

A 1-year old child was admitted with familial aHUS and a heterozygous loss of function mutation in complement factor H gene (3645C>T) and developed aHUS at 6 months of age.
Pediatric case

Aug 19, 2011 – 5 years of age

KIDNEY TRANSPLANT

ECULIZUMAB

PLASMA THERAPY

DIALYSIS

300 mg

PLATELET COUNT (10^3/microliter)

0 10 20 30 40 50

months

0 10 20 30 40 50 60 70 80 90 100 110

PLATELET COUNT (10^3/microliter)

0 50 100 150 200 250 300

Kidney Tx

600 300 600 300

0 1 7 14 days

300 300 300 300 300 300 300 300 300

1 2 3 4 5 months

Eculizumab (mg)
Pediatric case

Eculizumab levels microgr/ml

CH50 (normal range 79-187 Ueq/ml)

C5b-9 formed (pixel²)

Noris et al., Blood, 2014
Pediatric case

- **KIDNEY TRANSPLANT**
  - **ECULIZUMAB** 300 mg
  - **ECULIZUMAB** 600 mg

- **LIVER TRANSPLANT**
  - **ECULIZUMAB**
  - **ECULIZUMAB**

**PLASMA THERAPY**

**DIALYSIS**

**PLATELET COUNT (10^3/microliter)**

**C5b-9 formed (pixel²)**

**KDIGO**

Sept 18, 2014 – 8 years of age

Liver pre-Tx 600

Liver post-Tx 600

Liver post-Tx 600

Liver pre-Tx 600

Liver post-Tx 600

Liver Ecu STOP

Liver Ecu STOP

Liver Ecu STOP

Liver Ecu STOP

Liver Ecu STOP

Liver Ecu STOP
EAGLE Study
Evaluating the Morphofunctional Effects of Eculizumab* Therapy in Primary Membranoproliferative Glomerulonephritis:
A Pilot, Single Arm Study in 10 Patients with Persistent Heavy Proteinuria
and low C3 levels and high sC5b9 levels (>1000 ng/ml)

Elena Mondo, Piero Ruggenenti, Erica Daina, Marina Noris, Elena Bresin and Giuseppe Remuzzi

Unit of Nephrology, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy
Clinical Research Center for Rare Diseases “Aldo e Cele Daccò”, Mario Negri Institute for Pharmacological Research, Bergamo, Italy

* 900 mg weekly for four infusion and maintenance phase 1200 mg at week 5; then 1200 mg every 2 weeks for 1 years
THE REGISTRY OF STEROID RESISTANT NEPHROTIC SYNDROME

REGISTRY OF SRNS

Participating Centers 32
SRNS patients 274
Italian cases 235
Foreign cases 39

07/2015

http://www.marionegri.it
Rituximab in Steroid-Dependent or Frequently Relapsing Idiopathic Nephrotic Syndrome

Piero Ruggenenti,* † Barbara Ruggiero,* Paolo Cravedi,* Marina Vivarelli,† Laura Massella,† Maddalena Marasà,† Antonietta Chianca,* Nadia Rubis,* Bogdan Ene-lordache,* Michael Rudnicki,§ Rosa Maria Pollastro,‖ Giovambattista Capasso,‖ Antonio Pisani,‖ Marco Pennesi,** Francesco Emma,† † and Giuseppe Remuzzi,* † for the Rituximab in Nephrotic Syndrome of Steroid-Dependent or Frequently Relapsing Minimal Change Disease Or Focal Segmental Glomerulosclerosis (NEMO) Study Group
DERIVATION OF HUMAN iPSC-DERIVED PODOCYTES

Reprogramming* by 4 factors:
- Oct4
- Sox2
- Klf4
- cMyc

PBMC → iPSC cells

iPS cells → d0: Plating → d1: Mesoderm induction → d4: Renal precursors → d6 → d13: Mature podocytes

Synaptopodin/DAPI

Nephrin/DAPI
Synaptopodin WT-1

KDIGO
In vitro
15 days
Adaptative Designs: Examples

- **Ranking and selection designs**
  - “Pick-the-winner”, “drop-the-losers” designs are used for treatment/dose selection for a subsequent randomized study

- **Internal pilot designs**
  - The sample size is calculated during the pilot phase and patients of the pilot study are maintained in the subsequent trial

- **Sequential designs**
  - Continuous sequential analyses are planned with pre-set stopping criteria

- **Response-adaptative randomization designs**
  - Possibility to adapt the study design according to preliminary outcomes

 BALLS-IN-URN RESPONSE-ADAPTATIVE RANDOMIZATION DESIGNS

Probability of being allocated to experimental therapy

- **50%**
  - Experimental
  - Conventionall

- **66%**
  - Alive
  - Experimental ball added

- **75%**
  - Dead
  - Experimental ball added

  - Experimental
  - Conventional

- Black balls are added whenever a patient assigned to experimental therapy survives or one allocated to conventional therapy dies
- White balls are added whenever a patient assigned to experimental therapy dies or one allocated to conventional therapy survives
- The process continues until a preset stopping criterion is met

Gupta et al, J Clin Epidemiol, 2011
“The disease has contributed much more to science than science has contributed to the disease.”

— Jack Riordan
These slides belong to

Giuseppe Remuzzi, M.D.

Mario Negri Institute for Pharmacological Research, Bergamo, Italy.

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