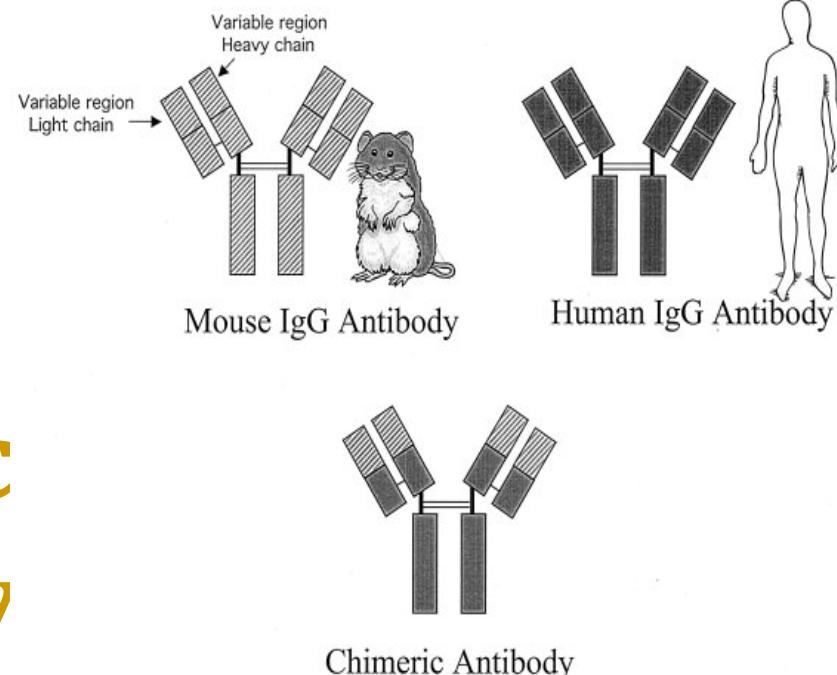


ASNIT day Roma , 2013

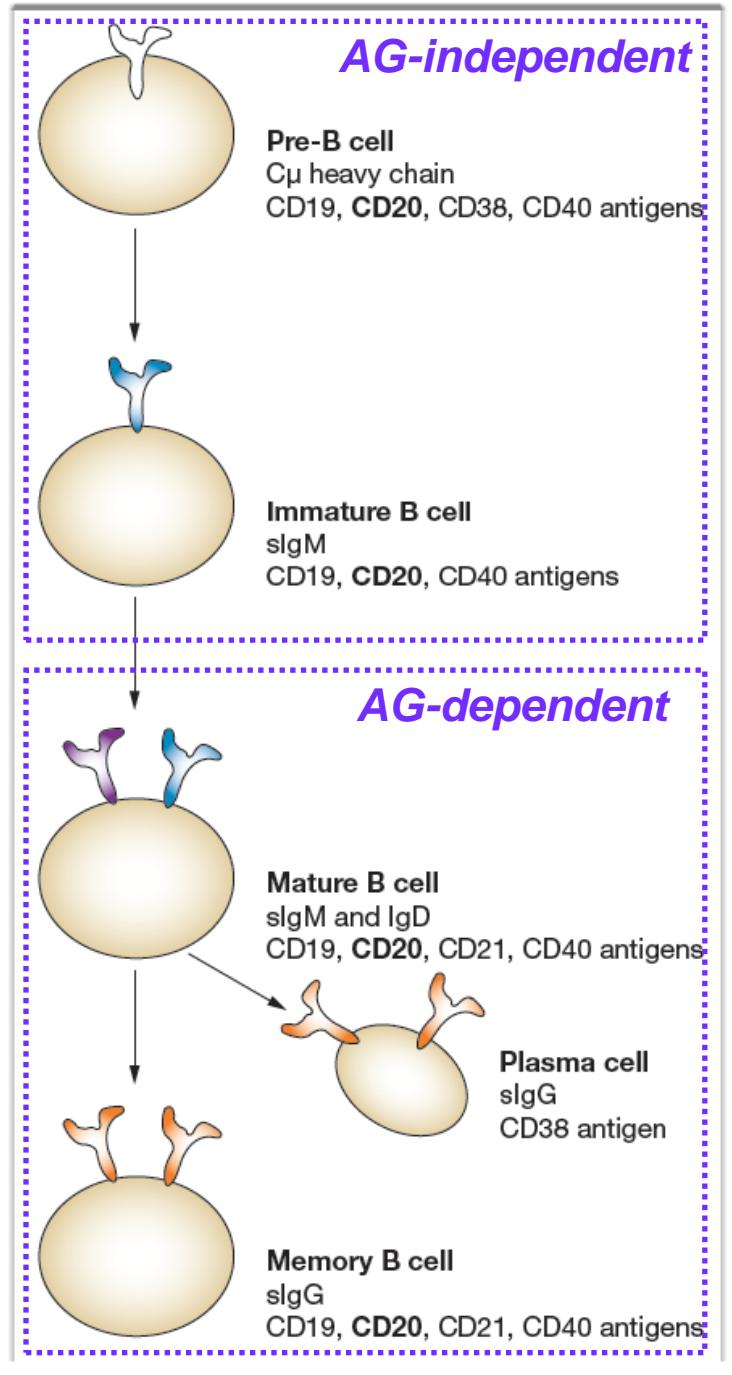
Gian Marco Ghiggeri



RTX is a Chimeric Antibody



- *Variable regions* from mouse IgG
- *Constant regions* from human (H) IgG1 and kappa (L)



CD20

297 AA (33-37 kD)

membrane-associated (surface AG) no shedding, no secretion

unclear function (calcium channel)
(proliferation and differentiation)

immature / mature B cells
on >85% NH cells

not on pro-B cells (CD19)

not on stem cells (CD34)

not on plasma cells

Anti-CD20

- Introdotto a fine anni 90 per il trattamento NH lymphoma
- Utilizzato successivamente nelle malattie autoimmuni con predominante componente humorale
- *Casualmente osservato un effetto sulla proteinuria in bambini con sindrome nefrosica secondaria a PTLD (Nozu, Pediatric Nephrol 2005; Pescovitz, NEJM 2006)*

Safety

- Used in one million of patients with hematologic malignancies (first line / maintenance)
- First infusion adverse reactions (bronchospasm, cough, chills, rash, fever, headache); mild / absent thereafter
- Recent systematic review in RCTs of RA treated with biologic therapy (N = 29,423): no increased risk of malignancies (Lopez-Olivo JAMA 2012)
- 23 cases of PML in > 500,000 patients; had either B-cell cancer (20) or lupus (3); all taking chemotherapy - no cases in MS / NS
- Anti-chimeric antibodies may develop / uncertain role

Terapia della SN con RTX

2005-2008

Pros- Evidenza di efficacia in singoli casi o piccole coorti

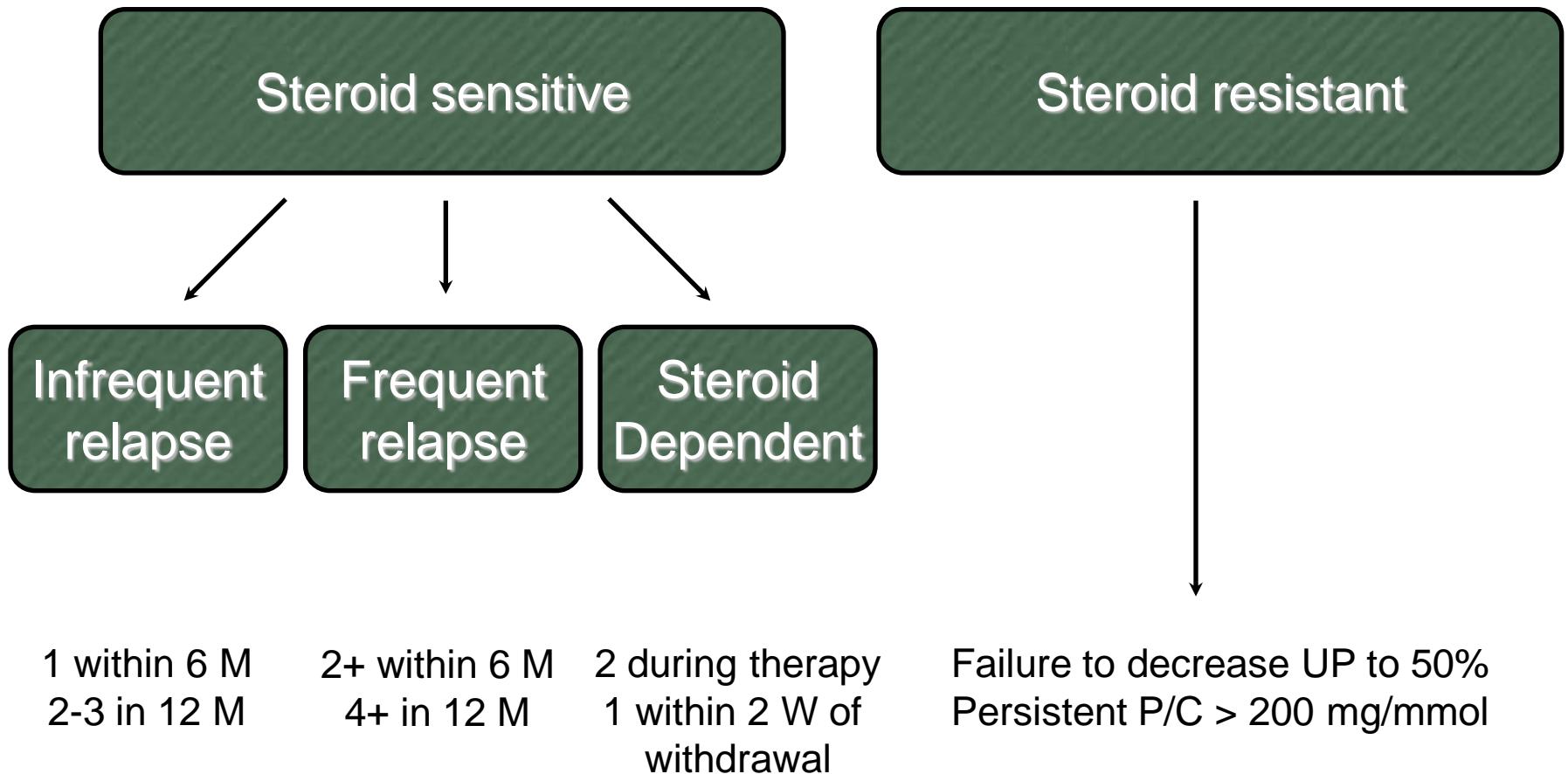
Cons- Inconsistenze sui meccanismi

Dubbi sui risultati

Effetti collaterali mutuati da altre patologie

Costi

FSGS



- Studi randomizzati (RCT)
- Studi prospettici
- Predizione degli effetti

RCT

TRY RESCUE

TheRapY of multidrug-RESistant nephrotic syndrome in ChildrEn with RitUXimab,

- 1- NS dependent to PDN and CNI (Ravani et al, cJASN 2011)
- 2- SRNS, (Magnasco et al, JASN 2012)
- 3- NS dependent to high levels of PDN, completed.
- 4- treatment of recurrence, ongoing.

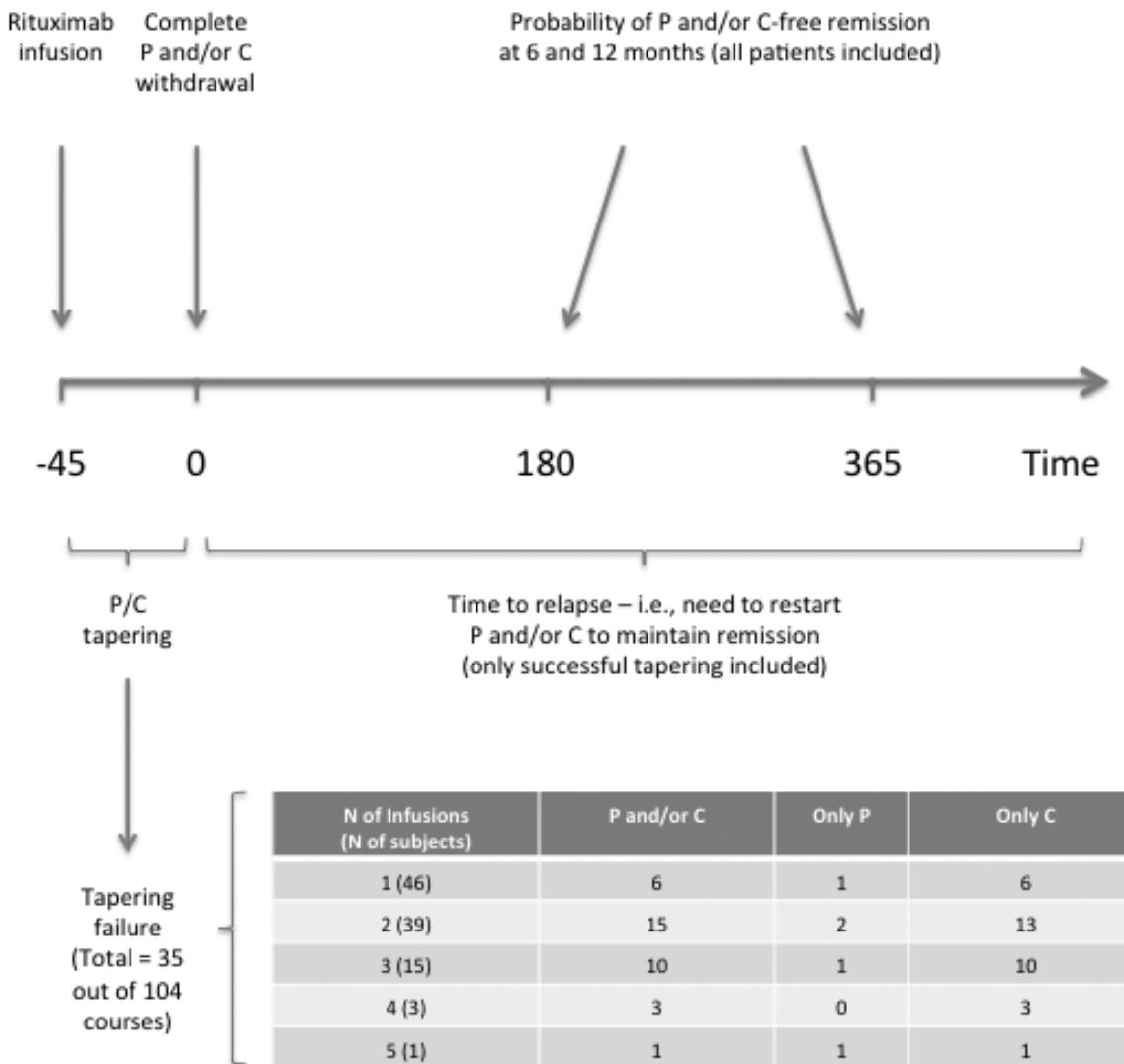
- RTX nella terapia della sindrome nefrosica resistente ai farmaci

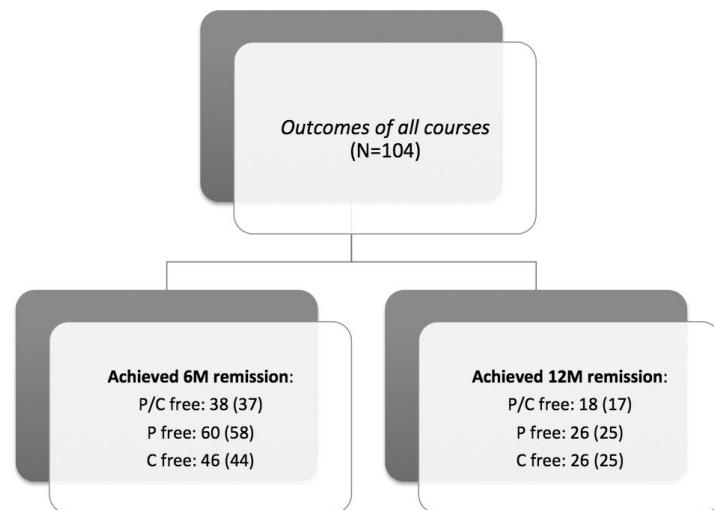
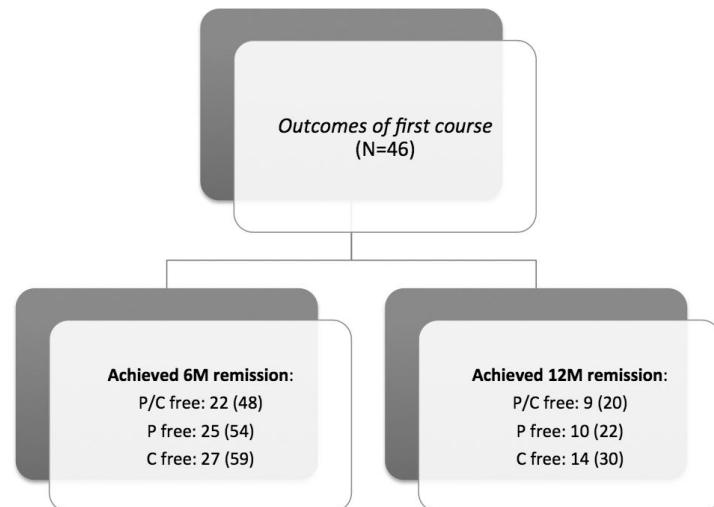
Delayed resistant

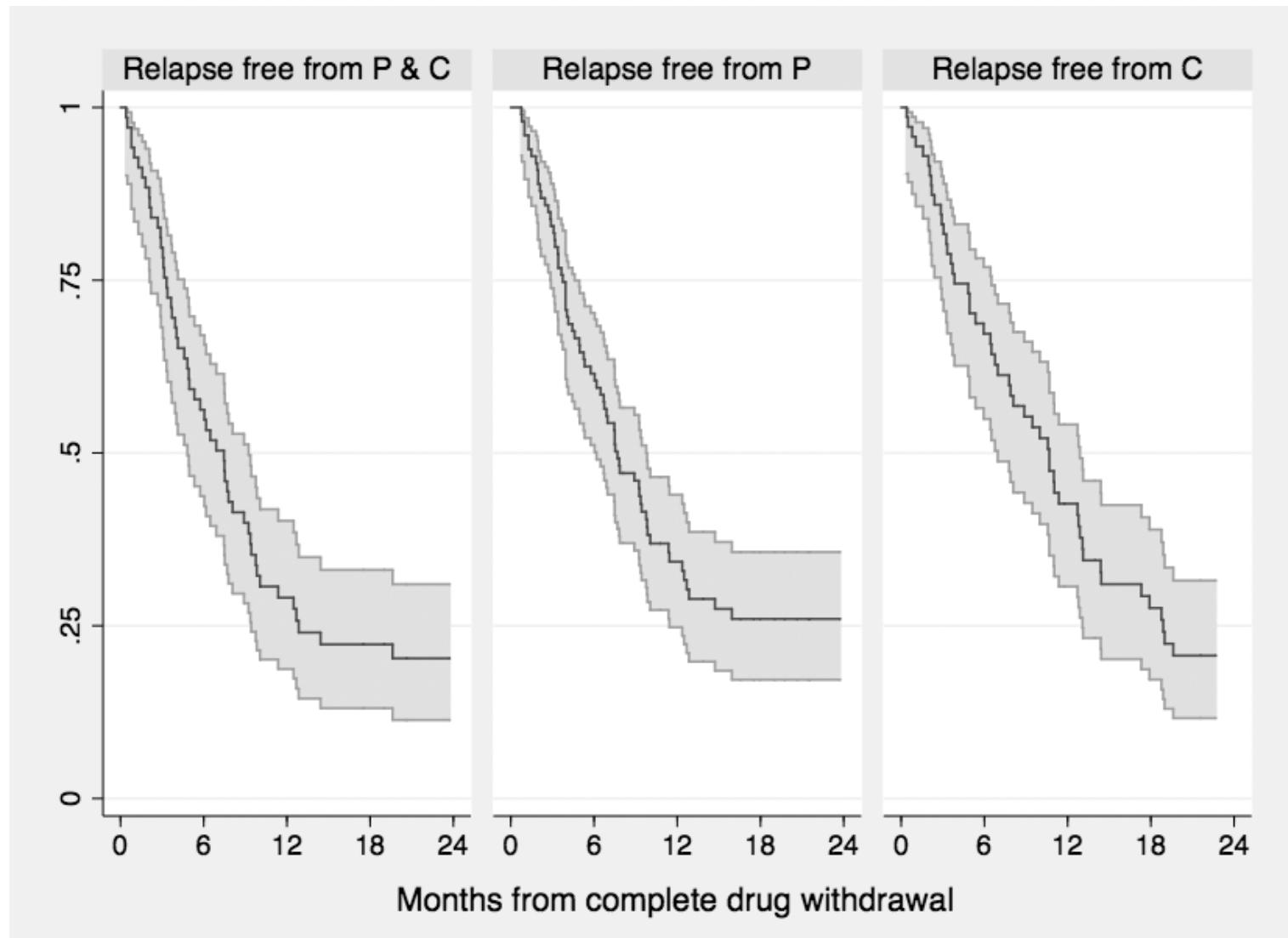
| | RTX (N=7) | | Control (N=8) | |
|-----------------------------|-------------------|-------------------|-------------------|-------------------|
| | T 0 | T 3 | T 0 | T 3 |
| Proteinuria (g/day)* | 1.9 (0.9, 3.8) | 0.5 (0.2, 1.6) | 1.8 (1.1, 3.2) | 0.9 (0.4, 2.7) |
| Serum Albumin (g/L) | 2.6 (±0.6) | 3.3 (±0.3) | 2.4 (±0.4) | 2.9 (±0.8) |
| Serum Creatinine (mg/dl) | 0.5 (±0.4) | 0.6 (±0.4) | 0.5 (±0.3) | 0.5 (±0.3) |
| Remission (n) | | 3 | | 3 |

RTX in NS sensibile alla duplice terapia

- Effetto delle dosi successive.
46 pazienti in follow-up 1-3 anni con
1-5 boli
- Terapia della recidiva







Adverse Events

- out of 104 treatments
- 5 pts required infusion in intensive care for initial broncospasm (speed dependent)
- 3 pts fever, skin rash, acute arthritis (2-4w)
- 2 pts neutropenia associated with viral infection

Lenght of remission after the first or subsequent cycles

| | First cycle | | Second and subsequent cycles | |
|---------------------|-------------|---------------------|------------------------------|---------------------|
| | Median | Interquartile range | Median | Interquartile range |
| Both P and C | 5.6 | 4.3 to 8.1 | 8.5 | 6.5 to 11.7 |
| Prednisone | 6.5 | 4.8 to 9.6 | 10.9 | 8.1 to 15.6 |
| CyA/FK506 | 7.3 | 5.6 to 10.2 | 11.6 | 8.9 to 15.8 |

Effect of age (per year) on the probability of remission

| | 6 months | | 12 months | |
|---------------------|-------------|---------------------|-------------|---------------------|
| | OR | 95% CI | OR | 95% CI |
| Both P and C | 1.71 | 1.11 to 2.62 | 1.31 | 1.04 to 1.65 |
| Prednisone | 1.23 | 1.05 to 1.45 | 1.19 | 1.06 to 1.32 |
| CyA/FK506 | 1.45 | 1.07 to 1.96 | 1.39 | 1.09 to 1.79 |

Adverse Events

- out of 104 treatments
- 5 pts required infusion in intensive care for initial broncospasm (speed dependent)
- 3 pts fever, skin rash, acute arthritis (2-4w)
- 2 pts neutropenia associated with viral infection

Prediction of effects

- ***FCGR2B* polymorphisms:** no variation
- ***FCGR3A* polymorphisms:** C allele Arg (P=0.059)
- **CD20 (*MS4A1*):** 1 mutation
- **SMPDL3b (*SMPDL3B*):** no mutation
- **Stress fibers/bleb formation analysis:** no effect

Ongoing studies

- TRY RESCUE 3: Efficacy of RTX in children with SDNS
- TRY RESCUE 4: Efficacy of RTX treatment of recurrence

TRY RESCUE 3

Efficacy of RTX in children with SDNS

Randomization n 30, A- n 15 RTX

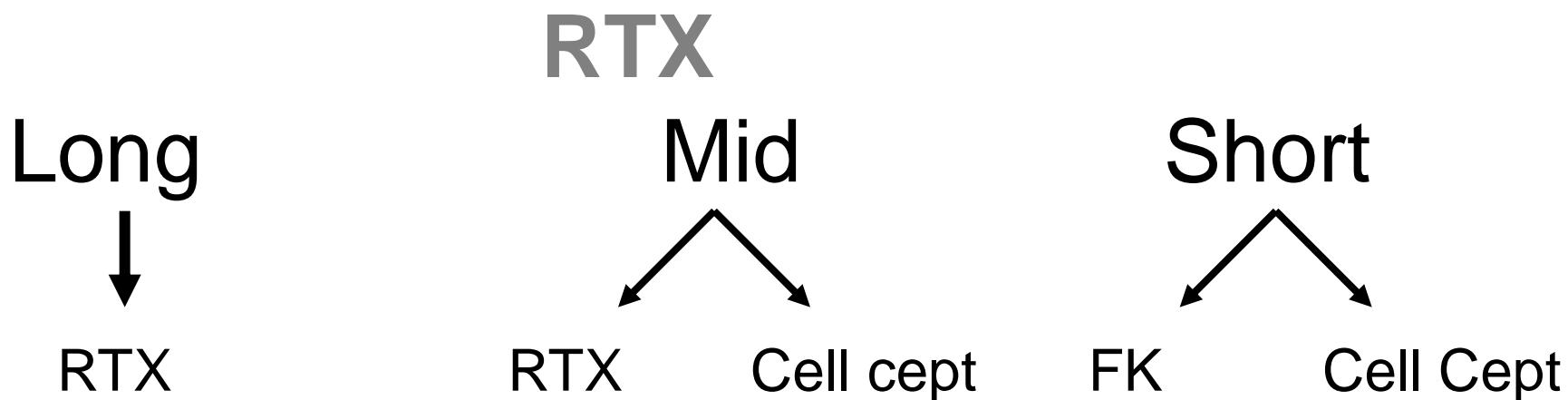
B- n 15 PDN

Follow-up 12 months

TRY RESCUE 4

Efficacy of RTX treatment of recurrence

Randomization n 81



CONCLUSIONI 1

- Le evoluzioni sulla terapia della SN dipendente a steroidi ed inibitori delle calcineurine sono soddisfacenti.
- Necessari test per predizione dell'effetto
- Si deve trovare un'efficace modello terapeutico per le recidive post-RTX

CONCLUSIONI 2

- La terapia delle forme resistenti varia in relazione al tempo di insorgenza della resistenza: early resistant peggio che late resistant.

CONCLUSIONI 3

- Ci sono evoluzioni sulla patogenesi: suPAR e citoscheletro/SMPDL
- Sono necessari ulteriori studi per chiarire il loro ruolo nella malattia e poterle utilizzare come marcatore surrogato di attività.

Thanks to:

- All people contributing to RTX studies
- G. Gaslini Medical Staff
- P. Ravani
- R. Gusmano
- The Kidney Foundation
- Wilma Querci Foundation



In memory of Prof R Gusmano