MANCHESTER 1824

The University of Manchester

NHS

Manchester University NHS Foundation Trust

Membranous Nephropathy and MN RADAR

Paul Brenchley

Director of Renal Research Labs

Manchester Royal Infirmary

RADAR Meeting

Feb 28th 2018, Birmingham

MANCHESTER 1824

The University of Manchester

NHS Manchester University NHS Foundation Trust

Milestones in understanding Membranous Nephropathy

THERAPY

PONTICELLI

MRC UK

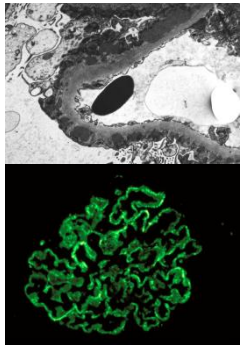
MENTOR

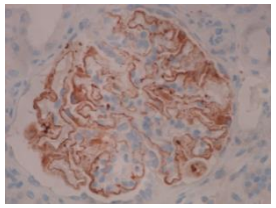
SCIENCE

MRC DNA

KRUK AUTOMN

Renal biopsy EM/ IF





THSD7A

GWAS in MN

PLA2R Epitope

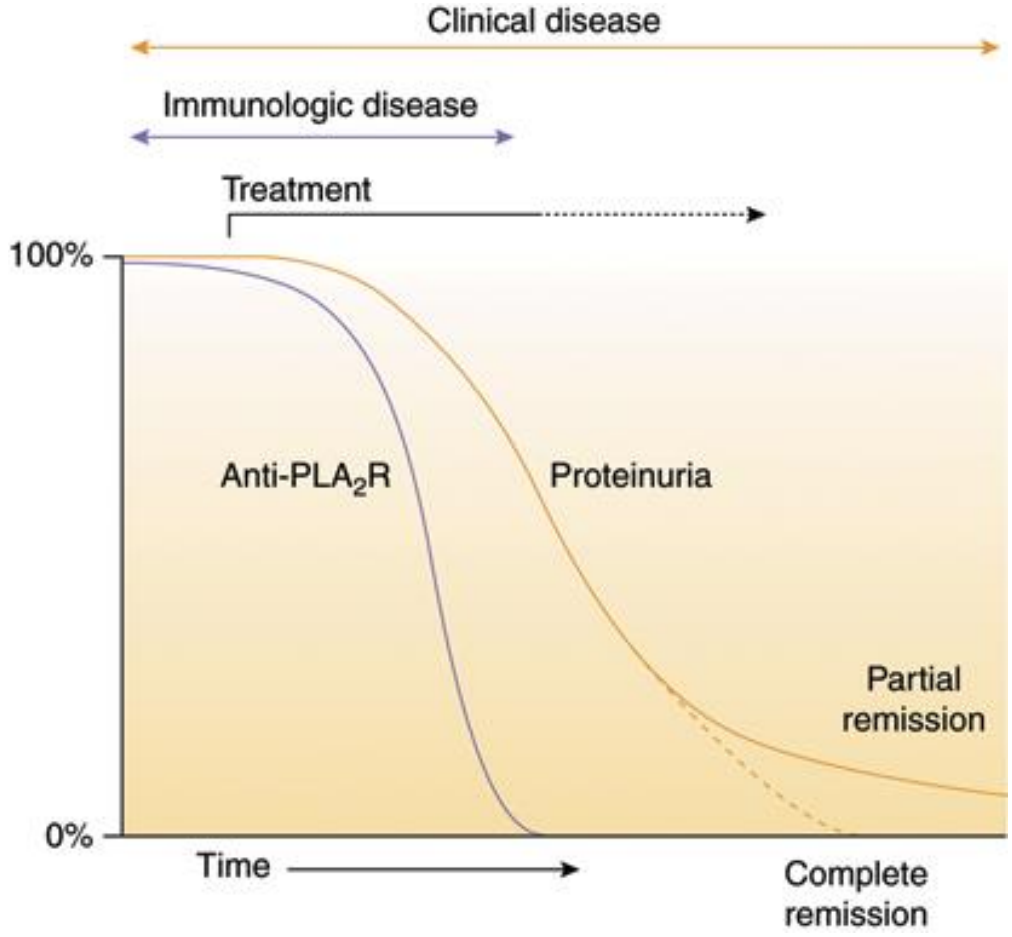
Megalin/GP330 antigen in PHN

1st MN antigen NEP

PLA2R antigen

1960 1990 2000 2010 2020

Relationship between clinical disease (proteinuria) and immunological activity (circulating anti-PLA2R) in IMN



Immunosuppressants

- Modified Ponticelli regime
- CSA
- Rituximab
- Belimumab

Membranous nephropathy: recent travels and new roads ahead. Laurence H Beck Jr and David J Salant Kid Int (2010)77: 765-770

MANCHESTER 1824

The University of Manchester

NHS Manchester University NHS Foundation Trust

MENTOR CLINICAL TRIAL 2013-2017 (Rituximab V CSA)

- **126 biopsied nephrotic MN cases** after 3 months randomised **to IV Ritux** (1gm 2 weeks apart; repeated at 6 months if reduction in proteinuria =/>25% **versus oral CSA** 3.5-5mg/kg/day for 6 months (continued for 6 months if reduction in proteinuria =/> 25%
- **Primary end point**: CR or PR at 24 months from randomisation
- **Secondary endpoints**:
  - relapse rate at 24 months after earlier CR or PR
  - anti-PLA2R levels
  - Quality of Life (KDQOL)
  - Adverse events
  - ESRD
  - CR or PR and CR alone at 6,12,18,24 months
  - time to CR or PR
  - effect on renal function (slope of Cr Clearance baseline to 24 months)

Fervensa FC et al Nephron (2015) 130:159-168

MN RADAR Registry

- 1500 MN patients consented since Autumn 2013
- Prospective follow up on clinical information from date of consent
- No clinical phenotype (autoantibody status/biopsy) at presentation or treatment history
- New wider consent for new patients from 2018
- MN RADAR as an electronic record for clinical trials/studies
- How to re-consent existing patients for links to
  - a) HES/ONS b) National clinical studies/trials ie MRC DNA Registry, AUTO-MN

NHS England CtE of Rituximab in Membranous Nephropathy (1)

Steering Group:

Arif Khwaja, Megan Griffith, Durga Kanigicherla, Lisa Willcocks, Jon Gulliver, Andy Hughes, Freddie Drew, Hannah Patrick, Hellen Powel, Anastasia Chalkidou, Mark Pennington, Bolaji Coker, Janet Peacock/Jennifer Summers, Steve Keevil , Richard Baker, Retha Steenkamp, Paul Brenchley, Phil Slater (NHS England, Renal Registry, NICE, KiTEC)

- **a prospective multi-centre national database (MN RADAR Registry) project 2018-2022 to obtain the evidence related to use of rituximab/biosimilars in MN**
- **to enable 180 patients to access rituximab treatment as part of a formal evaluation (non-routine commissioning) programme.**
- **prospective comparative data gathering (other immunosuppression) is not feasible.**
- **remission will be estimated and compared to published values.**
- **changes in continuous outcomes post treatment such as GFR, will be assessed within patient**

NHS England CtE of Rituximab in Membranous Nephropathy (2)

The primary question

how effective is rituximab and its biosimilars for the clinical indication covered within the CtE scheme in the following outcomes:

a) in the induction of remission (partial or complete) of nephrotic syndrome ?

b) in reducing the decline of renal function as measured by GFR?

Data collection

Demographics
Clinical assessment baseline
Clinical assessment baseline
Criteria for rituximab administration
Rituximab administration
Clinical assessment follow-up
Quality of life
Toxicity
Death

Goals for RADAR

Proof of concept ;

- **MN RADAR as the electronic case record for clinical trials**
- **Data linkage to HES and ONS**

MANCHESTER 1824

The University of Manchester

NHS Manchester University NHS Foundation Trust

Re-consenting the existing 1400 MN RADAR Patients?

To be usable in future clinical research, there needs to be a standard clinical presentation dataset on patients. This is missing as not entered when patients are entered into RADAR

Many patients will have participated in other valuable MN scientific/clinical studies

- **MRC DNA Bank (336) clinical data at presentation, GWAS data, serum antibody**
- **MRC TRIAL (120) clinical data at presentation and response to treatment**
- **MRC AUTO-MN (835) clinical data at presentation, GWAS, serum antibody**

MANCHESTER 1824

The University of Manchester

NHS
Manchester University
NHS Foundation Trust

How to access and link this data?

- Use advert on RPV and RADAR webpage about reconsenting and mail via Renal Unit
- Reconsent patients using the new consent which allows RADAR to contact patients
- Involve patients in completing the clinical presentation dataset?
- Do patients keep copies of their clinic letters -need first clinic summary letter?
- Patient data entry versus upload clinic letter?
- Questionaire to patients on involvement in other MN Clinical Studies?
- Seek permission through NHS Digital to link to historical databases?

MN RADAR - the next 10 years

CtE Rituximab →

Data linkage to MN studies (Historic) →

Future RCTs in MN →

RADAR cases and UKBIOBANK →