MEMBRANOUS GLOMERULONEPHRITIS

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Disclosure of Interests

- Alexion (research grant)
- Amgen (research grant)
- Roche (research grant)
- Amicus (consultancy)
We recommend that initial IS therapy be started only in patients with nephrotic syndrome AND one of the conditions below:

- Ur protein > 4g/d AND remains at >50% basal value, AND does not show progressive decline during antiproteinuric therapy during observation period > 6 months (1B)

- Severe, disabling, or life threatening symptoms related to nephrotic syndrome (1C)

- Scr has risen by >30% within 6 to 12 months from the time of diagnosis (but eGFR > 25-30 ml/min/1.73m²) and this change is not explained by superimposed complications (2C)
We recommend that initial therapy consist of a 6-month course of alternating monthly cycles of oral and i.v. corticosteroids, and oral alkylating agents (1B).

We suggest using cyclophosphamide rather than chlorambucil for initial therapy (2B).

We recommend that cyclosporine or tacrolimus be used for a period of at least 6 months in patients who choose not to receive the cyclical corticosteroid/alkylating-agent regimen or who have contraindications to this regimen.

*KDIGO Guidelines, Kidney Int 2012, 2:186*
KDIGO : Research recommendations

- Studies are needed to validate the utility of anti-PLA2R antibody in terms of its accuracy in separating primary from secondary MN.

- Studies are needed to determine the most cost-effective panel of investigations for screening an underlying (covert) malignancy in the older patients with MN.

KDIGO Guidelines, Kidney Int 2012, 2:186
Events since KDIGO 2012

- A wealth of studies on PLA2R
- Identification of THSD7A as a target
- Development of ELISA/IF tests (mostly EUROIMMUN)
- Two RCTs: GEMRITUX and MENTOR
- Retrospective comparisons of efficacy and safety (cyclophosphamide vs rituximab)
A paradigm shift in diagnostic, monitoring and classification of patients with MN

**PLA2R**

![Diagram of PLA2R domain structure]

- **CRD FN2D**
- **CTLD**
- **Putative PLA2 binding domain**

Conformational epitope is located in this region

- 31 mer peptide from this domain

**Thrombospondin type-1 domain containing 7A (THSD7A)**

![Diagram of THSD7A domain structure]

- **Trombospodin type-1 domains TSDs**

Beck et al, NEJM 2009, 361:11
Kao et al, JASN 2015, 26:291
Fresquet et al, JASN 2015, 26:302
Seitz et al, JASN 2016, 27:1517; JASN 2017 Nov 7th (epitope spreading correlated with outcome)

70% to 85% of adult MN patients

10 % of PLA2R-negative patients with MN

Tomas et al, J Clin Invest 2016, 126:2519
Serological tests for the diagnosis and monitoring of patients with MN

Indirect immunofluorescence for PLA2R and THSD7A

ELISA-PLA2R

Meta-analysis (2014)
- 15 studies, 2212 patients
- Specificity = 99%
  (95% CI: 96-100%)
- Sensitivity = 78%
  (95% CI: 66-87%)


Clinical disease
  - Initial disease
  - Remission
  - Relapse
  - Complete remission

Immunological disease
  - Partial remission

Anti-PLA2R

Proteinuria

Titer
Recommendations for a good usage of serological tests for PLA2R

- IF: screening test (more sensitive than ELISA, depends on cut-off ++)
- ELISA: monitoring
- But IF positivity persists longer, hence immunological remission requires negative IF
- Both IF and ELISA may be negative because of sink effect or immunological remission before any treatment

➡️ search for antigen in kidney biopsy
Antigen detection in biopsy is more sensitive than serology

Tenon cohort 2000-2014
- n = 106 (84 iMN；22 sMN)
- sensitivity PLA2R-Ag: 86%
- " aPLA2R-Ab: 76%


Retrospective diagnosis

PLA2R antigen is not specific for primary MN

Coincidence of iMN with the associated disease?

Lupus MN  HepB (25/39) Hep C  Sarcoidosis

The issue of cancer association with MN is not solved
A role for THSD7A in cancer-associated membranous nephropathy

Hoxha et al, NEJM 2016 374:1995
Prevalence of PLA2R and THSD7A-Ab in cancer patients

**Hamburg/Boston series**

Eight/40 patients with THSD7A-associated MN developed a malignancy within 3 months.

**Chinese series**

44 K-associated MN
- 1 THSD7A-Ab + (2%) Urinary bladder cancer > 7 years before MN
- 18 PLA2R-Ab + (41%) Time interval < 6 months in 10/18 patients

Toward a new serology/biopsy-based classification of MN

- PLA2R-related # 80 to 85%
- THSD7A-related <5%
- NonPLA2R-nonTHSD7A-related (third antigen) #10%

Any of the above can be:
- primary without known etiology
- secondary: PLA2R-associated HepB, sarcoidosis
  THDSD7A-(and PLA2R-) associated cancer

⚠️ Start with treatment of the suspected cause and shift to immunosuppresive therapy when needed
Specific treatment of (viral) cause may not cure secondary MN

Berchtold L et al, Kidney Int Reports, 2017, in press
Who and when to treat with immunosuppressive agents?

Can we shorten the 6-month « wait and see » period for patients at risk?
Is MN outcome still unpredictable?

- Evolution follows the 3-third rule (spontaneous remission, ESKD, persisting proteinuria and altered renal function)
- Clinical predictors: age, gender, degree of proteinuria, kidney function at presentation, time-varying proteinuria
- Quality of remission: CR vs PR (elevated relapse rates, Thompson et al, JASN 2015, 26:2930)
- PLA2R (and THSD7A) antibodies
High levels of PLA2R-Ab are correlated with:

- A lower rate of remission, either spontaneous or induced by IS treatment
- A higher risk:
  - of occurrence of nephrotic syndrome in non-nephrotic patients
  - of renal function deterioration
- A longer time to remission under IS treatment

Proportion of PLA2R-positive patients with remission is strongly dependent on antibody titer

Proportion of patients with complete or partial remission

HR (95%CI): 4.198 (1.919-9.185); p<0.0001
HR (95%CI): 2.298 (1.001-5.230); p=0.048

Patients at risk

<table>
<thead>
<tr>
<th>Tertile</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest Tertile</td>
<td>27</td>
</tr>
<tr>
<td>Middle Tertile</td>
<td>27</td>
</tr>
<tr>
<td>Highest Tertile</td>
<td>27</td>
</tr>
</tbody>
</table>

Revisiting algorithms for stratifying risks
MN treatment algorithm: The new approach

MN TREATMENT ALGORITHM

Mild UPro <4 g/day
RFTs normal
+ low PLA2R *

BP ≤125/75
ACEi/ARB
Monitor

* if +, monitor and consider PLA2R titer change
** risk reduction strategies
*** consider risk/benefit
# other options, see text

Moderate UPro (≥4 <8 d/day)
RFTs normal
+ mid PLA2R *

BP ≤125/75
ACEi/ARB Diet
Monitor 6/12

**Persistent ≥4 g/day

Cytotoxic + steroids or
CNI or
Rituximab

ACTH#

Heavy UPro ≥8 g/day
± RFTs

**Persistent ≥8 g/day ± RFTs

*** CNI or
*** Cytotoxic + steroids or
*** Rituximab

Catran and Brenchley, Kidney Int 2017, 91:566
What should be the first line therapy?

Efficacy vs safety: Is this still a timely question?

Time for a paradigm shift?
GEMRITUX protocol: 80 patients

Inclusion criteria:
- > 18 yrs
- idiopathic MN
- persisting NS after 6 months
- eGFR > 30 ml/min/1.73m²
- 2 determinations of proteinuria

Exclusion criteria:
- secondary MN
- pregnancy/breast feeding
- IS in the last 3 months (4 pts>1 yr)
- active infection

Dahan et al, JASN 2017, 28;348
Key findings from the GEMRITUX trial

PLA2R1-Ab

Clinical remission (last FU)

Dahan et al, JASN 2017, 28;348
Drawn by Ruggenenti et al, Nature Reviews 2017 July 3rd
Time to partial or complete remission (Per Protocol)

Cumulative incidence

Cyclosporine vs Rituximab

Number at risk
- Rituximab: 64, 46, 25
- Cyclosporine: 63, 35, 24

Months since randomization

0.00 0.25 0.50 0.75 1.00

0 6 12 18 24
Time to treatment failure (Per Protocol)

Cumulative incidence vs Months since randomization

- **Cyclosporine**
  - Number at risk: 63
  - Months: 0 (63), 6 (55), 12 (40), 18 (24), 24 (14)

- **Rituximab**
  - Number at risk: 64
  - Months: 0 (64), 6 (58), 12 (43), 18 (42), 24 (41)

<table>
<thead>
<tr>
<th>Time (Months)</th>
<th>Cyclosporine</th>
<th>Rituximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>63</td>
<td>64</td>
</tr>
<tr>
<td>6</td>
<td>55</td>
<td>58</td>
</tr>
<tr>
<td>12</td>
<td>40</td>
<td>43</td>
</tr>
<tr>
<td>18</td>
<td>24</td>
<td>42</td>
</tr>
<tr>
<td>24</td>
<td>14</td>
<td>41</td>
</tr>
</tbody>
</table>
## Analysis Per Protocol at 24 months

<table>
<thead>
<tr>
<th></th>
<th>CSA</th>
<th>RTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment failure</td>
<td>50 (79.4%)</td>
<td>24 (37.5%)</td>
</tr>
<tr>
<td>CR/PR</td>
<td>13 (20.6%)</td>
<td>40 (62.5%)</td>
</tr>
</tbody>
</table>

Strong evidence against the null hypothesis of inferiority (p-value <0.0001)

Risk Difference is 40.3% (95%CI 24.7% to 55.9%)

Odds Ratio is 6.0 (95%CI 2.7 to 13.2)
## Analysis Per Protocol at 24 months
(patients that were in C/PR at 12 months)

<table>
<thead>
<tr>
<th></th>
<th>CSA</th>
<th>RTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment failure</td>
<td>21 (63.6%)</td>
<td>1 (2.6%)</td>
</tr>
<tr>
<td>CR/PR</td>
<td>12 (36.4%)</td>
<td>37 (97.4%)</td>
</tr>
</tbody>
</table>

Strong evidence against the null hypothesis of inferiority (p-value <0.0001)

The estimated risk difference of being in remission between the RTX group and the Cyclosporine group is 43.856% (95% CI 28.409%, 59.302%)

The odds ratio of being in remission in the RTX group compared to the Cyclosporine group is 7.2065 (95% CI 3.1963, 16.2482)
Conclusion

- B cell targeting with Rituximab is as effective as Cyclosporine in inducing C/PR of proteinuria during active treatment phase
- B cell targeting with Rituximab is non-inferior to Cyclosporine in inducing long-term C or PR
- B cell targeting with Rituximab reduces the number of relapses and increases the time to relapse when compared with Cyclosporine
- B cell targeting with Rituximab has a better side effect profile
Have we made progress?

- Still 30 to 40% of patients do not achieve remission
- (Many) more partial remissions than complete ones
- Relapses more frequent in patients with partial remission
- Still severe adverse events, much less with rituximab
Toxicity is an important issue

- CPM gives a 3-fold increase in cancer risk, annually from 0.3 to 1.0% for the average patient (van den Brand et al, CJASN 2014, 9:1066)

- In a comparison between CPM (n=103) and RTX (n=100) with a FU of 40 months, the RTX group had less adverse events (63 vs 173), both serious (11 vs 46) and nonserious (52 vs 127), (van den Brand……Remuzzi, JASN 2017, on line)

- However CPM protocols differ between:
  
  Claudio Ponticelli (6 months, alternative therapy, 2.5 mg/kg)
  Jack Wetzels (6 to 12 months, continuous therapy, 1.5 mg/kg)
Comparison of safety and efficacy of RTX vs Steroids and Cyclophosphamide

van den Brand et al, JASN 2017, 28 : online

<table>
<thead>
<tr>
<th>Rates</th>
<th>RTX</th>
<th>St-CPM</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>70.6%</td>
<td>94.8%</td>
<td>0.01</td>
</tr>
<tr>
<td>CR</td>
<td>40.3%</td>
<td>41.5%</td>
<td>0.95</td>
</tr>
</tbody>
</table>
Immunological remission in PLA2R-Ab associated MN Steroids-CPM versus RTX (375 mg/m2, D1, D7)

van de Logt et al, ASN Renal Week 2017
Rituximab less effective at the used dose (375 mg/m2, D1, D7) in reducing aPLA2R after 6 months

van de Logt et al, ASN Renal Week 2017
How to monitor and predict clinical response and relapse?
PLA2R-Ab decrease precedes improvement of clinical parameters

**Serum Albumin**
\[ Y = 45.91 + 19.810 \cdot \ln(X) - 0.0124 + 0.179 \cdot (X^3 - 1.038) \]
Time to 50% increase = 11.4 months

**24-h Proteinuria**
\[ Y = -46.89 - 99.379 \cdot (X^{0.5} - 1.006) + 24.376 \cdot (X - 1.0125) \]
Time to 50% decrease = 10.5 months

**Anti PLA2R autoantibody**
\[ Y = -77.926 + 0.770 \cdot (X - 2.975) - 0.404 \cdot (X^3 - 1.038) \]
Time to 50% decrease = 0.65 months

PLA2R Ab titer increase or antibody re-emergence is associated with a high risk of relapse of the nephrotic syndrome

Unadjusted HR (95%CI): 7.68 (2.04-28.91); p=0.003
Adjusted HR (95%CI): 6.70 (1.68-26.81); p=0.007

Unadjusted HR (95%CI): 7.03 (1.80-27.44); p=0.0001
Adjusted HR (95%CI): 6.54 (1.57-27.14); p=0.010

Anti-PLA2R antibodies predict relapse rate after IS therapy

Therapeutic algorithm of membranous nephropathy: Look at kinetics of PLA2R-Ab!

Start IS
Follow PLA2R Ab titer bimonthly

Rapid PLA2R Ab response
>90% reduction <6m
Consider to stop IS

No PLA2R Ab response
<50% reduction at 6m
Modify IS

Slow PLA2R Ab response
50-90% reduction at 6m
Continue IS

De Vriese et al, JASN 2017, 28:421 (Mayo Clinic, California)

Should we wait for 6 months in pts with persisting high titers of PLA2R-Ab (and Ab spreading) until reinforcing/changing/combining therapy? Or consider 3 months as the turning point (GEMRITUX)?
Effect of rituximab on epitope reactivity in the GEMRITUX cohort

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Month 3</th>
<th>Month 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIAT</td>
<td>4</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>RTX</td>
<td>8</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>NIAT</td>
<td>9</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>RTX</td>
<td>12</td>
<td>15</td>
<td>19</td>
</tr>
</tbody>
</table>

P = 0.0001

Baseline: 11 patients, Month 3: 15 patients, Month 6: 19 patients

Seitz-Polski B, Debiec H..., Lambeau G, Ronco P, Nov. 7th 2017
Outcome of spreading (CysR C1/C7) in the GEMRITUX cohort

Spreading at baseline is associated with a decreased rate of remission at 6 months (OR 0.16, P = 0.02) and last follow-up (OR 0.14, P=0.01), irrespective of PLA2R-Ab titer at baseline.

Seitz-Polski B, Debiec H…, Lambeau G, Ronco P, Nov. 7th 2017
Changes in Treg in iMN patients treated with NIAT-Rituximab

Comparison of Treg at baseline

Rosenzwajg et al, Kidney Int. 2017 Mar 15
Our today practice at Tenon Hospital

- Shorten the « wait and see » period to 3 months in patients with high-level PLA2R-Ab persisting at 3 months
- Start with rituximab (RTX) as first-line therapy
- Retreat patients (re-infuse RTX) on the basis of PLA2R-Ab level, not CD19 depletion
- Use combined therapy (Prograf-RTX) in « refractory » patients
- Consider epitope spreading (epitope-specific ELISAs soon available)
Revisit definitions of remissions and relapse to better define therapeutic endpoints?

- Immunological remission should be defined by disappearance of PLA2R-Ab by IFT (remains positive longer than ELISA)
- Complete clinical remission is easy to define
- Partial remission (and relapse) relies on proteinuria which is highly variable
- PLA2R-Ab should be considered in the definition of disease remission
- Long-term complete remission without relapse remains the ultimate goal
- But treatment should first/also aim at immunological remission (complete) which usually precedes clinical remission by several weeks or months despite outliers (epitopes to be identified)
Unsolved questions and future challenges

- Understand remission/progression/recurrence
- Revisit MN classification based on antigens (causes are shared)
- Refine epitope analysis and replicate predictive value of spreading: delay treatment in patients with CysR-Ab only?
- Search for additional antigens
- Identify T-cell epitopes and replicate Treg data
- Develop anti-C5b-9 compounds
- Develop new treatment strategies (immunoabsorption, anti-B/plasma cell drugs) and combined therapies to fill the gap of the 30 to 40% failure
- Set large international trials with adaptive strategies
Proposed patterns of recurrence of membranous nephropathy according to PLA2R-Ab outcome

Gupta et al, Clin Transplant 2016, 30:461 ;
Debiec et al, Am J Transplant 2011, 11:2144
Assessment of risks of MN recurrence and progression post transplantation based on laboratory parameters obtained before and after transplantation.

Cosio et al, Kidney Int 2017, 91:304
Complete clinical remission required complete disappearance of PLA2R-Ab by IFT

Dahan et al Kidney Int Reports in press
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B. Seitz-Polski
V. Esnault

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G. Remuzzi
P. Ruggenenti
Nijmegen (NL)
J. Wetzels
J. Hofstra
UK
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Beijing (China)
MH. Zhao
Z. Cui
An indirect immunofluorescence assay for anti-THSD7A antibody (Euroimmun AG)

- 92% sensitivity and 100% specificity compared to Western blot
- Prevalence of THSD7A associated MN: 2.6% (prospective cohort of 345 patients)
- 40 patients with THSD7A-associated MN identified among 1276 patients with MN (retrospective and prospective, Hamburg and Boston cohorts)
- Eight patients developed a malignancy within 3 months
- Most patients were women

Hoxha et al JASN 2017, 28: 520
Epitope spreading as a new predictor

Coenen et al, JASN, 2013 24:677; Seitz-Polski et al, JASN 2016 27:1517

Frequent variants

- S87S
- M292V; H300D
- R404H

Rare variants

- CRD
- FNII

New variants

- NH2
- D200Y
- D272D
- R387C
- Y499C
- P600P
- V680L
- R387H
- L687P

Immunodominant epitope

CTLD

Splice site change
Exon 26 skipped

3 groups:
- CysR
- CysRC1
- CysRC1 C7 spreading increasing with age and proteinuria levels
Impact of spreading on renal function outcome

Seitz-Polski et al, JASN 2016 27:1517
A ten-year follow-up of the Ponticelli protocol (methylprednisone and chlorambucil)

Cumulative probability of survival without dialysis

- Treated Patients
- Untreated Patients

Probability of complete or partial remission

- Untreated controls
- Treated patients

P=0.0038

P=0.0000

Ponticelli et al, Kidney Int 1995, 48:1600
Cumulative probability of remission and relapse-free survival in patients given MP + Chlor. Vs MP + CPM

Ponticelli et al, JASN 1998, 9:444
# Severe adverse events

<table>
<thead>
<tr>
<th>Severe Adverse Events</th>
<th>Rituximab Group (N=37)</th>
<th>NIAT group (N=38)</th>
<th>no. of events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute renal failure</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostatitis</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Cardiac and vascular disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Critical limb ischemia</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Mesenteric Ischemia</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Carotid endarterectomy</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Acute hepatitis</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oedema</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>1</td>
<td>0</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>6</strong></td>
<td><strong>8</strong></td>
<td></td>
</tr>
</tbody>
</table>
Incidence of partial remissions is higher with cyclophosphamide

Rituximab:
Fewer (S)AE’s
Complete remissions ~
Renal failure ~
Partial remissions: ↓

van de Brand, JASN 2017
## Remission Status over time

<table>
<thead>
<tr>
<th></th>
<th>6 Months</th>
<th>12 Months</th>
<th>24 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CSA (n=63)</td>
<td>RTX (n=64)</td>
<td>CSA (n=63)</td>
</tr>
<tr>
<td>Complete Remission</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial Remission</td>
<td>31</td>
<td>23</td>
<td>13</td>
</tr>
<tr>
<td>≥25% Proteinuria reduction but not CR/PR</td>
<td>13</td>
<td>27</td>
<td>13</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>18</td>
<td>14</td>
<td>50</td>
</tr>
</tbody>
</table>
### Serious Adverse Events by SOC

<table>
<thead>
<tr>
<th>Category</th>
<th>CSA (n=65)</th>
<th>RTX (n=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac disorders</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Investigations</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Surgical and medical procedures</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total SAEs:</strong></td>
<td><strong>23</strong></td>
<td><strong>13</strong></td>
</tr>
</tbody>
</table>
Results 3: clinical remission rate after 6 months
Comparison of Treg and NK cells in IMN patients and healthy donors

HD: Healthy blood donors (n=27)
IMN: Patients (n=25)
Proposed patterns of recurrence of membranous nephropathy according to PLA2R-Ab outcome

Gupta et al, Clin Transplant 2016, 30:461 ;
Debiec et al, Am J Transplant 2011, 11:2144
Assessment of risks of MN recurrence and progression post transplantation based on laboratory parameters obtained before and after transplantation

Cosio et al, Kidney Int 2017, 91:304
Predictors of recurrence in a retrospective cohort of grafted patients with MN

- 113 pairs of donors/recipient:
  - 51 R: recurrence (kidney biopsy)
  - 62 WR: without recurrence (39 biopsy proven; 22 most likely with proteinuria < 0.5 g/day)
- Median time to R = 6 months; to last FU = 80 months
- Early (24 < 6 months) vs late recurrence (25 ≥ 6 months) and log-rank test for follow-up
- Determination of PLA2R status (serum or biopsy)
- Genetic studies (risk SNPs, allelotypes)
Clinical predictors of recurrence: cumulative probability of recurrence-free outcome

Gender
- Female recipient
- Male recipient

Living donor
- Deceased donor
- Living donor

N° of mismatches
- 0 to 2 HLA mismatch
- 3 HLA mismatch
- 4 HLA mismatch
- 5 to 6 HLA mismatch

PLA2R status
- PLA2R negative
- PLA2R positive

Berchtold et al. unpublished