KDIGO Controversies Conference on Glomerular Diseases 2017

A summary

Jürgen Floege

Division of Nephrology & Immunology
jfloege@ukaachen.de
KDIGO Controversies Conference on Glomerular Diseases

Jurgen Floege - Conference Co-Chair
Brad Rovin - Conference Co-Chair

General Principles, MPGN, C3GN
(Swell Room)

IgAN
(Galleria Ballroom)

Membranous GN
(Falcon Room)

MCD & FSGS
(Paradiso Room)

Lupus & ANCA
(Cardinal Room)

Breakout Group Co-Chairs

Catran (CA) Dan Barbour (CA) Sean Nachman (US) Patrick Gibson (US) Keisha Caster (US) Dawn
Hogan (US) Jonathan Tang (HK) Sydney Wetzels (NL) Jack Moeller (DE) Marcus Roccatallo (IT) Dario
Key Question: Which of the 2012 glomerular disease guideline may need revision?
General management of glomerular diseases
Kidney biopsy remains the cornerstone + likely to expand significantly in the near-term

Need for electron microscopy for every biopsy remains controversial

ACR and PCR helpful in general clinical management

Not sufficiently accurate for therapeutic decisions about using high-risk medications

eGFR equations not validated in specific glomerular diseases and patient populations

Floge J, ….. Rovin BH. Submitted
Change in Albuminuria and GFR as End Points for Clinical Trials in Early Stages of Chronic Kidney Disease

A Scientific Workshop Collaboration by the National Kidney Foundation, the European Medicines Agency and the U.S. Food and Drug Administration

March 15-16, 2018
• patient engagement in determining clinical trial eligibility
• patient-related outcomes and measurements rapidly evolving

• Newer determinants of progression: pre-maturity, sleep disturbances, obesity, genetics

• Hypertension + proteinuria: no news
• Uncertain: aldosterone or SGLT2 blockers; PCSK9 inhibitors and NOAC in nephrotic pts.
• multidisciplinary support, infection control
IgA-Nephropathy
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IgA Nephropathy – new options for therapy

- Targeted-release budesonide
- BAFF/APRIL inhibitors
- Cytokines
- Systemic circulation
- IgA+ ASC mistrafficking to systemic circulation
- Secretion of poorly galactosylated polymeric IgA1
- Genetic background
- Proteasome inhibitors
- BAFF/APRIL inhibitors
- Spleen tyrosine kinase inhibitor
- IgA+ IgA1 autoantibodies to IgA1 hinge region
- Immune complex formation
- Complement activation
- Eculizumab
- MASP-2 inhibitor
- Alternative pathway inhibitors
- Mesangial deposition
- Corticosteroids
- Spleen tyrosine kinase inhibitor
- Renal injury

Floeg J, ... Rovin BH. Submitted
The STOP-IgAN trial

Intensive Supportive Care plus Immunosuppression in IgA Nephropathy

Thomas Rauen, M.D., Frank Eitner, M.D., Christina Fitzner, M.Sc., Claudia Sommerer, M.D., Martin Zeier, M.D., Britta Otte, M.D., Ulf Panzer, M.D., Harm Peters, M.D., Urs Benck, M.D., Peter R. Mertens, M.D., Uwe Kuhlmann, M.D., Oliver Witzke, M.D., Oliver Gross, M.D., Volker Vielhauer, M.D., Johannes F.E. Mann, M.D., Ralf-Dieter Hilgers, Ph.D., and Jürgen Floege, M.D., for the STOP-IgAN Investigators*
Table 2. Serious Adverse Events and Adverse Events of Special Interest by Treatment Group

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Methylprednisolone (n = 136)</th>
<th>Placebo (n = 126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total SAEs</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>SAEs of infection</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>Respiratory infection</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Pneumocystis pneumonia</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Cryptococcal meningitis</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Nocardia infection</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Perianal abscess</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Fever</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Time From Randomization, mo

Patients Without SAE, %
Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN): a double-blind, randomised, placebo-controlled phase 2b trial

Bengt C Fellström, Jonathan Barratt, Heather Cook, Rosanna Coppo, John Feehally, Johan W de Fijter, Jürgen Floege, Gerd Hetzel, Alan G Jardine, Francesco Locatelli, Bart D Maes, Alex Mercer, Fernanda Ortiz, Manuel Praga, Søren S Sørensen, Vladimir Tesar, Lucia Del Vecchio, for the NEFIGAN Trial Investigators
Membranous GN

IgG

C3c

PLA2R
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Membranous GN – work-up + therapy

Pathogenically associated with concurrent disease

No

Yes

Nephrotic syndrome

PLA2R antibody

Positive

Negative

Risk assessment

Low risk

High risk

Kidney biopsy

No kidney biopsy

Non-immunosuppressive therapy

Immunosuppressive therapy

Floge J, … Rovin BH. Submitted
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## Membranous GN – immunosuppression

<table>
<thead>
<tr>
<th>Alkylating agents</th>
<th>Calcineurin inhibitors</th>
<th>Rituximab</th>
</tr>
</thead>
</table>
| • experienced physicians  
• restricted to pts at high-risk of progression | • induce remissions similar to cyclophosphamide, but greater likelihood of relapse | • **GEMRITUX**: rituximab more effective than placebo in inducing remissions  
• **MENTOR**: rituximab more effective than CyA in maintaining remission 24 months after enrollment; non-response rate to rituximab approximately 35% |

...It is likely that the choice of therapy may be determined by improved risk-stratification models incl. autoantibody levels ...

Floge J, …… Rovin BH. Submitted
Minimal Change Nephropathy

Focal Segmental Glomerulosclerosis

Parietal cell activation
“Steroid sensitive” and “steroid-resistant NS” should remain.

Term “primary/idiopathic FSGS” may require revision.

**Genetic testing:** patients with congenital/infantile forms of nephrotic syndrome, syndromic features, familial forms.

**Children:** Steroids first in all nephrotic pts; need for a global definition of “steroid resistance,” precise order of CYC, MMF, CNI and rituximab not well determined.

**Adults:** minimum 16 weeks of high-dose steroids as first-line therapy for FSGS or MCD controversial. CNIs or CYC second-line agents in adults with MCD. RTX emerging second-line therapy in MCD. CNIs and MMF second- and third-line treatments, resp., for FSGS.
Lupus erythematosus
### ISN/RPS classification
- does not consider tubulointerstitial injury, vascular lesions, or podocytropathies

### Genetic testing
- no clear clinical benefit from testing
- risks & benefits of \( \textit{APOL1} \) testing to be clarified

### Repeat renal biopsy
- patients with clinical remission can still have histologic activity and vice versa

### Prediction & Monitoring
- proteinuria at one year best predictor of long term renal outcome
- biomarker panels will be required to accurately stratify risk, predict flare, determine + monitor treatment, and predict prognosis
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### Lupus nephritis

<table>
<thead>
<tr>
<th>Treatment Type</th>
<th>Recommendation and Studies</th>
</tr>
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<tbody>
<tr>
<td>Antimalarials</td>
<td>• recommended for all patients with LN</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>• use at lowest possible dose during maintenance</td>
</tr>
<tr>
<td></td>
<td>• Low/zero-steroids protocols under investigation</td>
</tr>
<tr>
<td>CYC-/MMF-regimens</td>
<td>• remain the gold standard therapy for remission induction</td>
</tr>
<tr>
<td>Calcineurin-inhibitors</td>
<td>• Ongoing studies address role and toxicity in ethnically diverse populations</td>
</tr>
<tr>
<td>Maintenance Therapy</td>
<td>• minimum of 3 years, prolonged B-cell depletion with a RTX plus CYC may reduce the duration</td>
</tr>
<tr>
<td></td>
<td>• A repeat kidney biopsy may be helpful</td>
</tr>
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</table>

Rovin BH, … Floege J. Submitted
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**Refractory lupus nephritis**

<p>| | |</p>
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<tbody>
<tr>
<td>1</td>
<td>Verify adherence (check mycophenolic level if on MMF/check infusion records if on CYC)</td>
</tr>
<tr>
<td>2</td>
<td>Repeat biopsy if concern for chronicity or other diagnosis (?TMA, etc.)</td>
</tr>
<tr>
<td>3</td>
<td>Switch from MMF to CYC or vice versa</td>
</tr>
</tbody>
</table>
| 4 | Consider regimen with combined MMF/CNI ‘multi-target’ therapy *or*
|   | Addition of Rituximab *or*
|   | Consider prolonged course of IV pulse CYC |
| 5 | Consider intravenous IgG *or* plasmapheresis (especially in setting of concomitant TMA or refractory APS). *Minimal evidence outside of case reports* |

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Rovin BH, .... Floege J. Submitted
ANCA Vasculitis
### ANCA serology and Biomarkers

- MPO vs. PR3 ANCA has predictive value with respect to outcomes and risk of relapse
- New biomarkers:
  - Serum - CXCL 13, MMP-3, TIMP-1
  - Urine - soluble CD163
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ANCA vasculitides

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Severe ANCA vasculitides

Rapidly progressive ANCA-associated vasculitis

- > 4 mg/dl sCr or crescentic GN
- + Pulmonary hemorrhage

CYC with GCs
RTX with GCs
PLEX

Remission

Induction

Yes
AZA for at least 18 months
RTX on demand*
RTX on a fixed schedule

No
Refractory disease
Switching from CYC to RTX or vice versa

Maintenance

Taper AZA or stop RTX

Rovin BH, ..... Floege J. Submitted
**Refractory disease:**
- No improvement in 4 weeks
- Improvement of less than 50% in 6 weeks of treatment (as measured by BVAS/WG)
- Chronic persistent disease after more than 12 weeks

**Change in therapy:**
- Switch to RTX if previously treated with CYC (especially in PR3-ANCA patients) or vice versa
- Oral CYC if previous OV CYC failure (and RTX unavailable)
- IVIg 0.4 gr/kg for 5 days especially if persistent low disease activity

**Potential pitfalls**
- Vasculitis mimic?
- Adequate therapy?
- Symptoms related to:
  - Damage (ENT, proteinuria, neuropathy)
  - Infection
  - Cancer-related comorbidity
### Induction
- Four weekly intravenous doses of 375 mg/m²
- Four weekly intravenous doses of 375 mg/m² and 1 monthly infusion one and 2 months apart

### Maintenance
- 1000 mg every 6 months
- 1000 mg every 4 months
- 1000 mg every 6 months for 24 months
- 4 weekly doses of 375 mg/m² or two biweekly doses of 1000 mg, given on the basis of laboratory parameters
- 375 mg/m² every 6 months
- 1000 mg every 6 months
- 1000 mg every 12 months
- 500 mg on days 1 and 15, again every 6 mon for a total of 5 doses
Avacopan for ANCA vasculitis

➢ 67 pts with newly diagnosed or relapsing ANCA vasculitis
➢ All treated with cyclophosphamide or rituximab.