Treatment of IgA nephropathy: recent advances and prospect

Rosanna Coppo
Turin, Italy
In 1967 at the Actualités Néphrologiques de l’Hôpital Necker, glomerular IgA deposits were reported.

Berger J, Hinglais N. Intercapillary deposits of IgA-IgG. J Urol Nephrol (Paris) 1968
First targeted treatments aimed at reducing IgA levels: no effects of phenitoin no effect of tonsillectomy

several hits are needed for the development of IgA nephropathy
Transcriptomic and Proteomic Profiling Provides Insight into Mesangial Cell Function in IgA Nephropathy

Peidi Liu,* Emelie Lassén,* Viji Nair,† Celine C. Berthier,† Miyuki Suguro,† Carina Sihlbom,§ Matthias Kretzler,† Christer Betsholtz,¶ Börje Haraldsson,* Wenjun Ju,† Kerstin Ebefors,* and Jenny Nyström*

22 pathways are induced in mesangial cells by Galactose-deficient IgA1, most of which mediate inflammation
IgAN is an inflammatory disease:
corticosteroids have pronounced anti–inflammatory effects and rather weak immunosuppressive activity.

how to select patients that will benefit from corticosteroid therapy?
Oral prednisone (40 mg/d tapered over 1–2 years) in early phase of IgAN (GFR >70 ml/min and proteinuria of 1–2 g/day)

- reduction in proteinuria
- protection from functional decline at 10 years follow-up.
<table>
<thead>
<tr>
<th></th>
<th><strong>Pozzi [9]</strong></th>
<th></th>
<th><strong>Manno [10]</strong></th>
<th></th>
<th><strong>Lv [11]</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Steroid group</strong></td>
<td><strong>Control group</strong></td>
<td><strong>Steroid group</strong></td>
<td><strong>Control group</strong></td>
<td><strong>Steroid group</strong></td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>43</td>
<td>43</td>
<td>48</td>
<td>49</td>
<td>33</td>
</tr>
<tr>
<td><strong>Patient characteristics:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>38</td>
<td>40</td>
<td>31.8</td>
<td>34.9</td>
<td>27.8</td>
</tr>
<tr>
<td>Proteinuria (g/day)</td>
<td>2.0</td>
<td>1.8</td>
<td>1.7</td>
<td>1.5</td>
<td>2.5</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73 m²)</td>
<td>93</td>
<td>87</td>
<td>100.4</td>
<td>97.5</td>
<td>101.2</td>
</tr>
<tr>
<td>RASB during follow-up (%)</td>
<td>44%</td>
<td>40%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Follow-up duration (years)</td>
<td>4.0</td>
<td>4.0</td>
<td>4.8</td>
<td>5.3</td>
<td>2.2</td>
</tr>
<tr>
<td>Risk of experiencing the</td>
<td>5%</td>
<td>26%</td>
<td>14.8%</td>
<td>47.9%</td>
<td>3.4%</td>
</tr>
<tr>
<td>primary renal outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study design</td>
<td>Randomized, open-label, nonblinded</td>
<td></td>
<td>Randomized, open-label, nonblinded</td>
<td></td>
<td>Randomized, open-label, nonblinded</td>
</tr>
</tbody>
</table>
10.3.1: We suggest that patients with persistent proteinuría ≥1 g/d, despite 3–6 months of optimized supportive care (including ACE-I or ARBs and blood pressure control), and GFR >50 ml/min per 1.73 m², receive a 6-month course of corticosteroid therapy. (2C)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Corticosteroid regimen</th>
<th>Control regimen</th>
<th>Key outcome in steroid group versus control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pozzi et al., Italy²²,²⁴</td>
<td>Intravenous methylprednisolone 1 g/d for 3 consecutive days at the beginning of months 1, 3, and 5, plus oral prednisone 0.5 mg/kg every other day for 6 months</td>
<td>Supportive only</td>
<td>Ten-year renal survival = absent doubling of serum creatinine, 53% in controls versus 97% in the steroid group</td>
</tr>
<tr>
<td>Kato et al., Japan²⁰</td>
<td>Oral prednisolone 20 mg/d tapered to 5 mg/d at 18 months</td>
<td>Dipyramide</td>
<td>Significant reduction in proteinuría but not ESRD frequency</td>
</tr>
<tr>
<td>Hogg et al., United States²⁶</td>
<td>Oral prednisolone, every other day 60 mg/m² for 3 months, then 40 mg/m² for 9 months, and then 30 mg/m² for 12 months</td>
<td>Placebo</td>
<td>No benefit in the steroid group versus placebo at 2 years</td>
</tr>
<tr>
<td>Mano et al., Italy²⁵</td>
<td>Oral prednisolone for 6 months (1 mg/kg/day for 2 months, then reduced by 0.2 mg/kg/day per month)</td>
<td>Enalapril if hypertensive</td>
<td>Mean annual loss of GFR 6.2 ml/min in controls versus 0.6 ml/min in the steroid group</td>
</tr>
<tr>
<td>Lv et al., China²⁴</td>
<td>Oral prednisolone for 6–8 months (0.8–1 mg/kg/day for 2 months, then reduced by 0.2 mg/kg/day every 2 wk)</td>
<td>Supportive only</td>
<td>Significantly fewer patients with a 50% increase in serum creatinine in the steroid group</td>
</tr>
</tbody>
</table>

Therapeutic regimens and outcomes in randomized controlled trials in IgAN patients. RAS, renin-angiotensin system; ESRD, end-stage renal disease.

Relatively high-dose and short-term therapy (P>30 mg/day or high-dose i.v MP pulses for ≤1 year) produced significant renal protection, whereas low-dose, long-term steroid use did not.

(Lv J et al, JASN 2012)
Unmet needs and unanswered questions about the use of corticosteroids (CS) in IgAN

• Effectiveness of CS in patients with
- suboptimal renal function \((\text{eGFR}<50 \text{ ml/min})\)
- advanced CKD \((\text{eGFR}<30 \text{ ml/min})\)
- mild-moderate proteinuria \((>0.5 <1 \text{ g/day})\)

- different renal lesions (MEST scores)
- different clinical phases of activity (attack therapy versus maintenance therapy)

• Exhaustive attention and documentation of adverse events.
Corticosteroids in IgA Nephropathy: Lessons from Recent Studies

Rosanna Coppo

Validation of the Oxford classification of IgA nephropathy in cohorts with different presentations and treatments

Rosanna Coppo1,2, Stéphane Troyanov3,7, Shubha Bellur3,8, Daniel Cattran4,7, H. Terence Cook3,7, John Feehally6,7, Ian S.D. Roberts3,7, Laura Morando9, Roberta Camilla9, Vladimir Tesar9, Sigrid Lunberg9, Loreto Gesualdo6, Francesco Emma6, Cristiana Rollino6, Alessandro Amore9, Manuel Praga8, Sandro Feriozzi8, Giuseppe Segoloni8, Antonello Pani8, Giovanni Cancarini8, Magalena Durlík8, Elisabetta Moglia8, Gianna Mazzucco8, Costantino Giannakakis8, Eva Honsova8, B. Brigitta Sundelin9, Anna Maria Di Palma9, Franco Ferrario9, Eduardo Gutierrez9, Anna Maria Asuni9, Jonathan Barratt10, Regina Tardanico9, Agnieszka Perkowska-Ptasinska9 and on behalf of the VALIGA study of the ERA-EDTA Immunephrology Working Group8

Corticosteroids in IgA Nephropathy: A Retrospective Analysis from the VALIGA Study

Vladimir Tesar,*, Stéphane Troyanov,† Shubha Bellur,‡ Jacobien C. Verhave,‡ H. Terence Cook,§ John Feehally,† Ian S.D. Roberts,‡ Daniel Cattran,§ Rosanna Coppo,** and on behalf of the VALIGA study of the ERA-EDTA Immunephrology Working Group
Propensity-matched patients in VALIGA cohort: renal outcomes were better in Corticosteroid (CS) +RASB than RASB alone

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>RASB (184 cases)</th>
<th>RASB+CS (184 cases)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in proteinuria during entire follow-up (g/day)</td>
<td>-0.3 (-1.1, 0.3)</td>
<td>-0.8 (-1.6, -0.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Reduction proteinuria to &lt;1 g/day (%)</td>
<td>54%</td>
<td>84 %</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rate of renal function decline (mL/min/1.73m²/year)</td>
<td>-3.2± 8.3</td>
<td>-1.0 ± 7.3</td>
<td>0.004</td>
</tr>
<tr>
<td>ESRD (%)</td>
<td>20</td>
<td>7</td>
<td>0.003</td>
</tr>
<tr>
<td>Combined end-point 50% decrease in eGFR or ESRD (%)</td>
<td>27</td>
<td>12</td>
<td>0.008</td>
</tr>
</tbody>
</table>
Figure 2. Response to CS and RASB compared with RASB alone in propensity-matched individuals. (A) Entire propensity-matched cohort. (B) Stratified by initial eGFR. P values obtained using time-dependent Cox regression.
Changes in proteinuria in IgAN after corticosteroids.

Similar effects of corticosteroid pulse therapy in IgAN in different CKD stages
Predictive value of time average proteinuria (follow-up proteinuria)
(survival from 50% decrease in eGFR and/or ESRD)

TAP <0.5 g/day vs 0.5 to 0.9 g/day: p<0.001
TAP 0.5 to 0.9 g/day vs 1.0 to 1.4 g/day: p= 0.001
TAP 1.0 to 1.4 g/day vs 1.5 to 1.9 g/day: p= 0.04

Number at risk

<table>
<thead>
<tr>
<th>Proteinuria Range</th>
<th>Number</th>
<th>Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.5 g/day</td>
<td>338</td>
<td>97 (29%)</td>
</tr>
<tr>
<td>0.5-0.9 g/day</td>
<td>315</td>
<td>77 (24%)</td>
</tr>
<tr>
<td>1.0-1.5 g/day</td>
<td>167</td>
<td>46 (28%)</td>
</tr>
<tr>
<td>1.5-1.9 g/day</td>
<td>108</td>
<td>14 (13%)</td>
</tr>
</tbody>
</table>

Coppo et al  VALIGA  2014  Kidney Int
Figure 3. Response to CS and RASB compared with RASB alone in propensity-matched individuals stratified by proteinuria during follow-up, prior to CS in the CS-RASB group. (A) Proteinuria <1 g/d. (B) Proteinuria 1 to <3 g/d. (C) proteinuria ≥3 g/d. Time-average proteinuria was prior to CS in the treated group. P values obtained using time-dependent Cox regression. There was no evident benefit of CS in those with a proteinuria <1 g/d.
Benefits of CS in addition to RASB in IgAN patients with proteinuria >1 g/day, even with an initial eGFR <50 ml/min/ 1.73 m². CS benefits extended to CKD 3-4.

No rapid benefits when proteinuria <1g/day, but need of long term follow-up.

Questions still open about Corticosteroids in IgAN:
- suboptimal renal function (eGFR<50 ml/min)
- advanced CKD (eGFR<30 ml/min)
- mild-moderate proteinuria (>0.5 <1 g/day)
Persistent proteinuria > 0.75 g/day, <3.5 g/day is spite of 6 months of comprehensive supportive care

- supportive care alone
- supportive care with the addition of immunosuppressive therapy

a) eGFR of > 60 ml/min: 6 months glucocorticoid (9 x 1g IV MP pulses) + OP 0.5mg/kg.eod

b) eGFR > 30 < 59 ml/min: 3 years immunosuppression: cyclophosphamide 1.5 mg/kg for 3 months, followed by azathioprine 1.5 mg/kg for months 4-36 plus oral prednisolone 40 mg/day, tapered to discontinuation at month 36
full clinical remission:
<0.2 UP/Ucr with stable eGFR (decrease in eGFR < 5 ml/min /1.73 m²)

decrease in the eGFR of at least 15 ml/min /1.73 m²
Effects of Two Immunosuppressive Treatment Protocols for IgA Nephropathy

Thomas Rauen, Christina Fitzner, Frank Eitner, Claudia Sommerer, Martin Zeier, Britta Otte, Ulf Panzer, Harm Peters, Urs Benck, Peter R. Mertens, Uwe Kuhlmann, Oliver Witzke, Oliver Gross, Volker Vielhauer, Johannes F.E. Mann, Ralf-Dieter Hilgers, and Jürgen Floege

A. In Full Clinical Remission

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Events</th>
<th>Total No.</th>
<th>Odds Ratio (97.5% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High-GFR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supportive Care</td>
<td>3/54</td>
<td>11/55</td>
<td>5.31 (1.07-26.36)</td>
<td>0.02</td>
</tr>
<tr>
<td>Corticosteroid Monotherapy</td>
<td>3/51</td>
<td>11/47</td>
<td>3.36 (1.1-26.28)</td>
<td>0.018</td>
</tr>
<tr>
<td><strong>Low-GFR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supportive Care</td>
<td>1/26</td>
<td>3/27</td>
<td>3.52 (0.26-55.89)</td>
<td>0.302</td>
</tr>
<tr>
<td>Immunosuppressive Combination Therapy</td>
<td>1/21</td>
<td>3/24</td>
<td>2.24 (0.16-30.72)</td>
<td>0.491</td>
</tr>
</tbody>
</table>

GFR Decrease at least 15 ml/min/1.73 m²

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Events</th>
<th>Total No.</th>
<th>Odds Ratio (97.5% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High-GFR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supportive Care</td>
<td>16/54</td>
<td>12/55</td>
<td>0.64 (0.24-1.75)</td>
<td>0.324</td>
</tr>
<tr>
<td>Corticosteroid Monotherapy</td>
<td>14/52</td>
<td>10/53</td>
<td>0.63 (0.22-1.8)</td>
<td>0.318</td>
</tr>
<tr>
<td><strong>Low-GFR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supportive Care</td>
<td>6/26</td>
<td>9/27</td>
<td>1.67 (0.41-6.79)</td>
<td>0.415</td>
</tr>
<tr>
<td>Immunosuppressive Combination Therapy</td>
<td>4/24</td>
<td>7/25</td>
<td>1.79 (0.37-8.64)</td>
<td>0.41</td>
</tr>
</tbody>
</table>
The STOP-IgAN trial

- Was powered to detect differences in clinical remission, which did it in favour of CS/IS. Changes of proteinuria during the follow-up need a long observation to produce effects on GFR decline protection

- Small changes in eGFR 15 ml/min are not a valid surrogate end-point. The RCT was too short and underpowered to detect established outcomes like 50% change in eGFR
The STOP-IgAN trial is the best evidence yet that adding an aggressive immunosuppressive regimen to aggressive kidney-protective therapies provides some benefit after 3 years of treatment (e.g., greater likelihood of complete remission of proteinuria and clearing of microscopic hematuria) but at a substantial cost (infection and one death from sepsis).

Isabelle Ayoub, Lee Hebert, Brad H. Rovin, M.D.
Effect of Oral Methylprednisolone on Clinical Outcomes in Patients With IgA Nephropathy
The TESTING Randomized Clinical Trial
TESTING RCT

- Proteinuria > 1 g/day in spite of 3 months of optimized RASB supportive care,
- eGFR 20 to 120 mL/min/1.73m².
- Randomized to oral methylprednisolone (0.6-0.8mg/kg/day) or placebo for 2 months, then weaning over 4 to 6 months.

- 262 participants randomized (eGFR, 59 mL/min, proteinuria 2.40 g/d) followed over a median of 2.1 years

recruitment was discontinued because of excess serious adverse events.
15% in methylprednisolone group vs 3.2% in placebo (P = .001) mostly due to serious infections (8.1% vs 0; P < .001), including 2 deaths.

- Primary renal outcome (ESRD or a 40% decrease in eGFR)

in 6% in methylprednisolone group vs 16% in placebo group (P = .02)
Figure 4. Effect of Methylprednisolone Therapy on eGFR and Proteinuria During Follow-up

A. eGFR

<table>
<thead>
<tr>
<th>Time From Randomization, mo</th>
<th>Methylprednisolone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>60, 55</td>
<td>50, 45</td>
</tr>
<tr>
<td>6</td>
<td>55, 50</td>
<td>45, 40</td>
</tr>
<tr>
<td>12</td>
<td>50, 45</td>
<td>40, 35</td>
</tr>
<tr>
<td>18</td>
<td>45, 40</td>
<td>35, 30</td>
</tr>
<tr>
<td>24</td>
<td>40, 35</td>
<td>30, 25</td>
</tr>
<tr>
<td>30</td>
<td>35, 30</td>
<td>25, 20</td>
</tr>
<tr>
<td>36</td>
<td>30, 25</td>
<td>20, 15</td>
</tr>
</tbody>
</table>

No. of patients:
- Methylprednisolone: 135, 117, 103, 93, 55, 23
- Placebo: 123, 109, 99, 88, 55, 23

B. Urinary protein

<table>
<thead>
<tr>
<th>Time From Randomization, mo</th>
<th>Methylprednisolone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3.0, 2.5</td>
<td>2.5, 2.0</td>
</tr>
<tr>
<td>6</td>
<td>2.5, 2.0</td>
<td>2.0, 1.5</td>
</tr>
<tr>
<td>12</td>
<td>2.0, 1.5</td>
<td>1.5, 1.0</td>
</tr>
<tr>
<td>18</td>
<td>1.5, 1.0</td>
<td>1.0, 0.5</td>
</tr>
<tr>
<td>24</td>
<td>1.0, 0.5</td>
<td>0.5, 0.0</td>
</tr>
<tr>
<td>30</td>
<td>0.5, 0.0</td>
<td>0.0, 0.0</td>
</tr>
<tr>
<td>36</td>
<td>0.0, 0.0</td>
<td>0.0, 0.0</td>
</tr>
</tbody>
</table>

No. of patients:
- Methylprednisolone: 135, 117, 103, 93, 55, 23
- Placebo: 123, 109, 99, 88, 55, 23
## Adverse events (AE) and renal function

<table>
<thead>
<tr>
<th>Renal function</th>
<th>AE in CS alone</th>
<th>AE in CS+azathioprine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1 (Lancet 1999)</td>
<td>2.3%</td>
<td>-</td>
</tr>
<tr>
<td>eGFR 90 ml/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 2 (JASN 2010)</td>
<td>5.7%</td>
<td>16.8%</td>
</tr>
<tr>
<td>eGFR 81 ml/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 3 (JN 2013)</td>
<td>15.4%</td>
<td>30.0%</td>
</tr>
<tr>
<td>eGFR 34 ml/min</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**STOP**
Rauen et al., NEJM 2015
33% of patients eGFR < 60 ml/min

**TESTING**
Lv et al., JAMA 2017
38.5% of patients eGFR < 50 ml/min

(Sarcina C and Pozzi C, CJASN 2016)
Patients enrolled in all the RCTs were selected only on the basis of persistent proteinuria >1 g/day

histopathology was not considered (active versus sclerotic lesions)
The MEST score provides earlier risk prediction in IgA nephropathy

Sean J. Barbour\textsuperscript{1,2,3}, Gabriela Espino-Hernandez\textsuperscript{2}, Heather N. Reich\textsuperscript{4}, Rosanna Coppo\textsuperscript{5}, Ian S.D. Roberts\textsuperscript{6}, John Feehally\textsuperscript{7}, Andrew M. Herzenberg\textsuperscript{4,8} and Daniel C. Catran\textsuperscript{4}; for the Oxford Derivation, North American Validation and VALIGA Consortia

901 IgAN from
the Oxford Classification study (167 cases)
North American validation study (87 cases)
VALIGA validation study (647 cases)
Primary outcome (50% decrease in eGFR or ESRD).
Figure 3 | The receiver operating curves for models predicting the 5-year risk of a 50% reduction in estimated glomerular filtration rate (eGFR) or end-stage renal disease (ESRD) using clinical data at biopsy with or without MEST, and 2-year clinical data alone. AUC, area under the curve.
Patients with M0 and T0 have low risk even if UP 1-1.5 g/day
Patients with M1 and UP at biopsy < 1g/day are at high risk
### Outcomes in propensity score matched IgAN patients with MST lesions

<table>
<thead>
<tr>
<th></th>
<th>RASB</th>
<th>Corticosteroids+RASB</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>M1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR yearly loss ml/min/y</td>
<td>-6.1</td>
<td>-1.8</td>
<td>0.001</td>
</tr>
<tr>
<td>Final proteinuria &lt; 1 g</td>
<td>57%</td>
<td>80%</td>
<td>0.008</td>
</tr>
</tbody>
</table>
Evidence from the Oxford Classification cohort supports the clinical value of subclassification of focal segmental glomerulosclerosis in IgA nephropathy

Shubha S. Bellur\textsuperscript{1}, Fanny Lepeytre\textsuperscript{2}, Olga Vorobyeva\textsuperscript{1}, Stéphan Trojanov\textsuperscript{2}, H. Terence Cook\textsuperscript{3} and Ian S.D. Roberts\textsuperscript{1}; on behalf of the International IgA Nephropathy Working Group

\begin{figure}
\centering
\begin{subfigure}{0.4\textwidth}
\centering
\includegraphics[width=\textwidth]{image1.png}
\caption{Segmental sclerosis and podocyte hypertrophy}
\end{subfigure}
\begin{subfigure}{0.4\textwidth}
\centering
\includegraphics[width=\textwidth]{image2.png}
\caption{Glomerular tip lesion}
\end{subfigure}
\begin{subfigure}{0.4\textwidth}
\centering
\includegraphics[width=\textwidth]{image3.png}
\caption{Capsular adhesion}
\end{subfigure}
\begin{subfigure}{0.4\textwidth}
\centering
\includegraphics[width=\textwidth]{image4.png}
\caption{Perihilar segmental sclerosis and hyalinosis}
\end{subfigure}
\end{figure}
Evidence from the Oxford Classification cohort supports the clinical value of subclassification of focal segmental glomerulosclerosis in IgA nephropathy

Shubha S. Bellur, Fanny Lepeytre, Olga Voroljan, S.D. Roberts; on behalf of the International

Podocyte hypertrophy or tip lesions are markers of podocyte injury and in untreated patients are associated with

• proteinuria increase
• worse prognosis
In these patients without corticosteroid treatment, E1 score was predictor of worse renal survival. HR 4.75, p<0.001
A Multicenter Study of the Predictive Value of Crescents in IgA Nephropathy


Pooled data: Oxford, VALIGA, China and Japan cohorts (3096 patients, 36% with crescents)

![Graph showing the distribution of the percentage of glomeruli with crescents in biopsies with any crescents. Crescents were present in 1118 (36%) of 3096 total biopsies.]

Crescents correlated with E1 and were associated with immunosuppressors.
Crescents were predictive of combined event, but only in patients not receiving immunosuppressors.
Oxford Classification of IgA nephropathy 2016: an update from the IgA Nephropathy Classification Working Group

Hernán Trimarchi, Jonathan Barratt, Daniel C. Catran, H. Terence Cook, Rosanna Coppo, Mark Haas, Zhi-Hong Liu, Ian S.D. Roberts, Yukio Yuzawa, Hong Zhang and John Feehally on behalf of the IgAN Classification Working Group of the International IgA Nephropathy Network and the Renal Pathology Society; for Conference Participants

MEST-C :
C0: no crescents
C1 < 25% of glomeruli
C2 25% or more glomeruli with crescents
Is it time to design new RCTs, looking for personalized treatments of IgAN considering pathology lesions?
Mycophenolate Mofetil Combined With Prednisone Versus Full-Dose Prednisone in IgA Nephropathy With Active Proliferative Lesions: A Randomized Controlled Trial

Jin-Hua Hou, MD, Wei-Bo Le, PhD, Nan Chen, MD, Wei-Ming Wang, PhD, Zhang-Suo Liu, MD, Dong Liu, PhD, Jiang-Hua Chen, MD, Jiong Tian, PhD, Ping Fu, MD, PhD, Zhang-Xue Hu, MD, Cai-Hong Zeng, PhD, Shao-Shan Liang, MD, Min-Lin Zhou, MD, Hai-Tao Zhang, MD, and Zhi-Hong Liu, MD

- proteinuria >1.0 g/24 h, eGFR >30 ml/min
- biopsy within 1 month
- crescents (>10 <50% of glomeruli)
- endocapillary hypercellularity or glomerular necrosis
- tubular atrophy/interstitial fibrosis <50%

- Primary end point: rate of complete remission at 6-12 months (UP undetectable, Cr,not >25% baseline).
- Secondary end points: time to remission and changes in active proliferative lesions on a repeat biopsy.

MMF+ prednisone half doses versus full-dose prednisone did not differ in reducing proteinuria, but fewer adverse events with similar results.
Patients at risk of progression thought to benefit from corticosteroids:
- Persistent proteinuria > 3 g/day (**)
- Persistent proteinuria > 1 g/day (*)
- Proteinuria < 1 g/day with M1 or E1 or S1 with podocytopathy or when C 1- C2 (§)

Addition of corticosteroids to supportive care induces reduction in proteinuria possible reno-protective effects on the long term (**)
Benefits also when GFR < 50 ml/min71.73m2 (*)
Increase in adverse events but mostly in cases with impaired renal function (**)

For all patients with IgAN and proteinuria > 0.75 < 3.5 g/day:
- Rigorous supportive care targeting RAS, dysmetabolism and lifestyle

Addition of corticosteroids to supportive care therapy needed?

- No when proteinuria 0.75-1.5 g/day and negative MEST scores (§)
- Yes when IgAN is in progression with rapid loss of GFR (**)
- Yes when risk factors are present (**)
Patients enrolled in all the RCTs were selected only on the basis of persistent proteinuria >1 g/day

Histopathology was not considered
(active versus sclerotic lesions)

Rapidity of progression over the previous weeks/months was not considered
(fast versus indolent course)
sCr > 1.5 mg/dl, worsening e-GFR & expected ESRD in 5 years proteinuria 4-4.8 g/day.

Prednisone for 2 years, cyclophosphamide for 3 months, azathioprine for 2 years
Why, when and how should immunosuppressive therapy considered in patients with immunoglobulin A nephropathy?

**Progressive course of IgAN and RPGN-IgAN**

- Progressive decrease of renal function (ΔGFR > 3 ml/min within 3 months or > 12 ml/min per year or > 10% increase of serum creatinine within 3 months) or refractory high proteinuria > 1 g/day or crescents in renal biopsy and normal kidney size and eGFR > 10 ml/min

**I: CyC pulses with steroid pulse therapy and high dose orally corticosteroid Induction (month 1-2)**

**M: MPA with low dose prednisolone**
Should we in the future continue to expose patients with IgAN to the systemic effects of steroids?
involvement of intestinal mucosal immunity in the pathogenesis of IgAN: focus on the gut-kidney axis
Activation of intestinal immunity in IgAN: subclinical intestinal mucosa inflammation leading to IgA dysregulated synthesis.

Sites of mucosal B cell induction: lower ileum and ascending colon with high density of Peyer’s patches.

target release formulation of the glucocorticoid budesonide: coated starch capsules for site-specific drug delivery at the ileo-cecal junction.
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

www.thelancet.com Published online March 28, 2017 http://dx.doi.org
targeting intestinal mucosal immunity
A Randomized, Controlled Trial of Rituximab in IgA Nephropathy with Proteinuria and Renal Dysfunction


Figure 2. eGFR trends in (A) rituximab versus (B) control groups. The red line represents average data.

failed to show after 1 year any improvement in eGFR, proteinuria, Gd-IgA1 or anti-Gd-IgA1 antibody levels
CD20-CD19+ CD27high plasmocytes/plasmablasts express IgA, the mucosal cell adhesion molecule β7 integrin and the mucosal chemokine receptor CCR10

B cells resident in the mucosa are not deleted by Rituximab

Rituximab is not useful in ulcerative colitis
targeting intestinal mucosal immunity
Factors controlling the switch to IgA:
TNF family members
B cell activator factor
BAFF (BlyS)
APRIL

Critical role for IgA production
**Clinical data**

**Experimental evidence**

Serum BAFF is increased in IgAN patients

BAFF promotes proliferation of mesangial cells

Mice overexpressing BAFF develop a commensal flora–dependent, IgA-associated nephropathy


PLOS ONE

**Pathogenetic Role of a Proliferation-Inducing Ligand (APRIL) in Murine IgA Nephropathy**

Yang Gyun Kim, Montserrat Alvarez, Hitoshi Suzuki, Sachiko Hirose, Shozo Izui, Yasuhiro Tominoh, Bertrand Haard, Yusuke Suzuki
**Clinical Trials. Gov**

NCT02062684  
**BRIGHT-SC: Blisibimod Response in IgA Nephropathy Following At-Home Treatment by Subcutaneous Administration**  
**Target: BAFF**

**Interventions**

- drug: Blisibimod;
- drug: Placebo

Phase 2 BRIGHT-SC study of blisibimod in 58 patients with IgAN. Interim analysis

Patients were treated for up to 2 years, with at least 60 weeks of treatment.

- **Blisibimod:** no change in proteinuria with slight decline
- **Placebo:** increase in proteinuria

**Interventions**

- drug: Atacicept 25 mg
- drug: Placebo

**Target: TACI**
Spontaneous IgAN mouse model expressing human IgA1 and CD89 (double transgenic alpha1KI-CD89Tg mice)

The complexes IgA1-CD89 interact with transferrin 1R (TfR1/CD71) and transglutaminase 2 (TG2)
Gluten free diet for 3 generations

- Reduction in:
  - IgA1 mesangial deposition
  - Glomerular inflammatory-cell infiltration
  - IgA1–sCD89 complexes in serum and kidney eluates
  - Hematuria

Gluten diet for 30 days

Intestinal injury
(inflammation and villous atrophy)

Increase in:
- IgA1–sCD89 complexes
- IgA1 mesangial deposition
- IgA1 antigliadin Ab
- Correlation with proteinuria
Correlation between anti-gliadin antibodies and proteinuria in experimental alpha1KI-CD89 mice on gluten diet.
Early gluten-free diet abolishes IgAN development, hematuria and proteinuria in alpha1KI-CD89Tg mice
Gluten-induced experimental IgA glomerulopathy

Figure 2. Semiquantitative analysis of IgA immune deposits in BALB/c mice after 14 wk of different diets.
MAY GLUTEN-FREE DIET REDUCE THE LEVELS OF IgA IMMUNE COMPLEXES IN PRIMARY IgA NEPHROPATHY?
R Coppo, B Basolo, C Rollino, D Roccatello, G Martina, A Amore, *G Bongiorno, G Piccoli
University of Turin Nephrology and Dialysis Unit, *Dietetic Service, S Giovanni Hospital, Turin, Italy

Figure 4. Effects of a gluten-free diet on the levels of IgAIC in IgAGN patients.

Dietary Antigens and Primary Immunoglobulin A Nephropathy
Conclusion of early studies (30 years ago)
to target gluten for treating patients with IgAN

- **Gluten-free diet** was of some benefit in our exploratory study (29 patients without evidence of celiac disease) with reduction of proteinuria, but without effect on renal function decline after 4 years.

- The gluten-free diet is difficult to be followed without gastrointestinal symptoms

- RAS inhibition became an easy therapeutic choice and the diet was abandoned

Need of a new RCT testing gluten-free diet in IgAN
Genetic factors for the control of intestinal barrier & GALT response

Epigenetic factors: exposure to alimentary components (gluten) and/or intestinal microbiota dysbiosis microbe products (LPS)

Increased intestinal permeability

GALT response subclinical inflammation

Galactose deficient IgA1 (deGal IgA1)

antigen loaded dendritic cells

IgA mesangial deposits IgAN

inflammatory mediators

IgAIC

IgG anti deGal IgA1

The gut-kidney axis in IgA nephropathy

Coppo R
NDT 2015
treat key mediators!
Complement activation in IgAN as a biomarker of activity and progression

Current Understanding of the Role of Complement in IgA Nephropathy

Nicolas Maillard,*† Robert J. Wyatt,† Bruce A. Julian,* Krzysztof Kiryluk,9 Ali Gharavi,9 Veronique Fremeaux-Bacchi,† and Jan Novak*

Hit 1
- Increased circulating galactose-deficient IgA1

Hit 2
- Production of unique antiglycan antibodies

Hit 3
- Formation of pathogenic IgA1-containing circulating immune complexes

Hit 4
- Mesangial deposition and mesangial cells activation leading to glomerular injury

Mesangial cells have an active role in complement activation
Lectin and alternative pathways are activated and contribute to tissue injury
Association of C4d Deposition with Clinical Outcomes in IgA Nephropathy

Mario Espinosa, Rosa Ortega, Marina Sánchez, Alfonso Segarra, Maria Teresa Salcedo, Fayna González, Rafael Camacho, Miguel Angel Valdivia, Rocío Cabrera, Katia López, Fernando Pinedo, Eduardo Gutierrez, Alfonso Valera, Miryam Leon, María Angeles Cobo, Rosa Rodríguez, José Ballarín, Yolanda Arce, Beatriz García, María Dolores Muñoz, and Manuel Praga for the Spanish Group for the Study of Glomerular Diseases (GLOSEN)

C4d deposits in IgA nephropathy: where does complement activation come from?

Rosanna Coppo

Mesangial C4d Deposits in Early IgA Nephropathy

Alfonso Segarra,1 Katheryne Romero,1 Irene Agraz,1 Natalia Ramos,1 Alvaro Madrid,2 Clara Carnicer,3 Elias Jatem,4 Ramón Vilalta,2 Luis Enrique Lara,2 Elena Ostos,4 Naiara Valtierra,4 Julianna Jaramillo,1 Karla V. Arredondo,1 Gema Ariceta,2 and Cristina Martinez5

Defective gene expression of the membrane complement inhibitor CD46 in patients with progressive immunoglobulin A nephropathy

Eculizumab treatment for rescue of renal function in IgA nephropathy

Therese Rosenblad · Johan Rebetz · Martin Johansson · Zivile Békássy · Lisa Sartz · Diana Karpman
Targeting the complement cascade: novel treatments coming down the pike

Joshua M. Thurman¹ and Moglie Le Quintrec²

A diagram illustrating the complement cascade with annotations for various components and potential inhibitors. The text below the diagram reads: "A review of drugs that target the complement cascade. Complement activation is initiated through the following..."
Open-label pilot Phase 2 trial in Sweden and the USA

Presented as oral communication at ERA-EDTA 2017 meeting

Some encouraging early results
IgA1 Protease Treatment Reverses Mesangial Deposits and Hematuria in a Model of IgA Nephropathy

Sebastian M. Lechner,†‡§ Lilia Abbad,†‡§ Erwan Boedec,†‡§ Christina Papista,†‡§ Marie-Bénédicte Le Stang,†‡§ Christelle Moal,†‡§ Julien Maillard,†‡§ Agnès Jamin,†‡§ Julie Bex-Coudrat,†‡§ Yong Wang,‖ Aiqun Li,‖ Paolo G.V. Martini,‖ Renato C. Monteiro,†‡§ and Laureline Berthelot†‡§

J Am Soc Nephrol:

**Figure 1.** Decrease in serum IgA1 levels and mesangial IgA1 deposits after IgA1-P treatment. (A) IgA1 deposit detection in the mesangium (brown) after IgA1-P IV injection (1, 3, and 10 mg/kg) in α1KI-CD89Tg mice (n=3 mice per group) using immunohistochemistry directed against human IgA on frozen kidney sections. Representative sections. (B) Concentrations of serum IgA1 after IgA1-P injection for each time point of euthanized mice as described in (A). (C) Detection of IgA1 fragments by western blot in serum from mice after 3 mg/kg injection. Representative samples of selected time points. (D) Pharmacokinetics (PK) of IgA1-P in serum of α1KI-CD89Tg mice after IV injection for each time point of euthanized mice as described in (A). PD, pharmacodynamics.
Mucosal immunity

Gal deficient GdIgA1 (hit 1)

IgG anti GdIgA1 (hit 2)

IgA1 immune complexes formation and renal deposition (hit 3)

complement activation

activation of mediators and renal injury (hit 4)

hematuria, proteinuria

progressive damage and loss of kidney function

MALT-targeted drugs

diet and microbiota

anti B cell therapies

protease to remove IgA

complement inhibitors

mediators (IL-6, STAT3) inhibition

pathology (MEST) and activity targeted therapies

diet and microbiota

protease to remove IgA
15th International Symposium on IgANephropathy

IIGANN 2018

September 27th-29th, 2018 - The Brick Hotel, Buenos Aires, Argentina

https://www.iigann2018.com
Merci de votre attention