Current clinical trials in treating IgAN

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Renal Division, Peking University First Hospital
Characterized by dominant IgA glomerular deposits.

Clinical presentation: highly variable

Histologic features: glomerular, tubular, interstitial, and vascular lesions

Clinical course: variable course

The mechanisms responsible for development of IgAN are incompletely understood, and this has limited development of highly targeted therapies for this disease.
**Intervention** | **Recommendation** | **Grade**
---|---|---
**Blood pressure control and use of ACE inhibitors or ARBs** | Long-term use of ACE inhibitors or ARBs is recommended for patients with proteinuria > 1g/day, with up-titration of the drug depending on blood pressure to achieve proteinuria <1g/day. A target blood pressure of <130/80 mm Hg is recommended for patients with proteinuria <1 g daily, and <125/75 for patients with proteinuria >1 g daily. | 1B

**Corticosteroids** | A 6-month trial of corticosteroids is recommended in patients with persistent proteinuria of >1g/day despite 3–6 months of optimal supportive care and GFR > 50 ml/min per 1.73m². | 2C

**Other immunosuppressive agents** | Patients with crescentic IgAN involving over 50% of glomeruli and rapidly progressive course should be treated with steroids and cyclophosphamide. Not treating with corticosteroids combined with cyclophosphamide or azathioprine (unless crescentic forms with rapidly progressive course). Not using immunosuppressive therapy in patients with GFR < 30 ml/min per 1.73 m² (unless crescentic forms with rapidly progressive course). Not using MMF | 2D

**Fish oils** | Fish oils may be potentially useful in patients with persistent proteinuria ≥ 1g/d, despite 3–6-months of optimized supportive care. | 2D

**Tonsillectomy** | Not recommended | 2C
<table>
<thead>
<tr>
<th>No.</th>
<th>Intervention</th>
<th>Design</th>
<th>Sample size</th>
<th>Expected complete</th>
<th>Sponsor/Location</th>
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</thead>
<tbody>
<tr>
<td>NCT01758120</td>
<td>Prednisone plus cyclophosphamide</td>
<td>RCT-open label</td>
<td>120</td>
<td>2015 Dec</td>
<td>Guangdong General Hospital/China</td>
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<tr>
<td>NCT01854814</td>
<td>Mycophenolate Mofetil</td>
<td>RCT-open label</td>
<td>232</td>
<td>2018 Jun</td>
<td>Nanfang Hospital/China</td>
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<tr>
<td>NCT00318474</td>
<td>Mycophenolate Mofetil</td>
<td>RCT-Double Blind</td>
<td>184</td>
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<td>St. Joseph's Hospital and Medical Center/ USA.</td>
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<tr>
<td>NCT00657059</td>
<td>Mycophenolate Mofetil</td>
<td>RCT-open label</td>
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<td>2013 Jun</td>
<td>Sun Yat-sen University/China</td>
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<td>NCT02981212</td>
<td>Mycophenolate Mofetil</td>
<td>RCT-open label</td>
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<td>2018 Oct</td>
<td>Yonsei University/Korea</td>
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<td>NCT03188887</td>
<td>Corticotherapy</td>
<td>RCT-Double Blind</td>
<td>122</td>
<td>2019 Jun</td>
<td>Assistance Publique Hôpitaux de Paris/France</td>
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<tr>
<td>NCT00554502</td>
<td>Stop-IgAN</td>
<td>RCT-open label</td>
<td>148</td>
<td>2013 Dec</td>
<td>RWTH Aachen University/Germany</td>
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<tr>
<td>NCT01560052</td>
<td>TESTING Study</td>
<td>RCT-Double Blind</td>
<td>750</td>
<td>2017 Sep</td>
<td>Peking University/China</td>
</tr>
</tbody>
</table>
STOP-IgAN (German)  
TESTING Study (International)  
NEFIGAN Trial (Europe)
STOP-IgAN: Study-Design

IgAN, 18-70 years old, GFR > 30 ml/min, proteinuria > 0.75 g/d plus hypertension or GFR < 90 ml/min

Optimal supportive therapy
(ACEi, ARB, target BP < 125/75 mm Hg, Statin, etc.)
Baseline after 6 months: BP, proteinuria, GFR

Responder
Proteinuria <0.75 g/d
optimal supp. therapy;
periodic proteinuria checks

Proteinuria >0.75 g/d

Non-Responder
Proteinuria >0.75 g/d

GFR ≥ 60 ml/min
Steroids for a total of 6 months (methylprednisolone in bolus plus oral prednisolone)

Cyclophosphamide (1.5 mg/kg/d p.o.) for 3 months
Azathioprine (1.5 mg/kg/d)
Steroids (40 mg/d reduce to 7.5 mg/d)

GFR 30-59 ml/min

Optimal supportive therapy
(n=74)

Optimal supportive + immunosuppression
(n=74)

Responder after 6 months: BP, proteinuria, GFR

Dropout
Proteinuria > 3.5 g/d
GFR-Loss > 20%
# 3-Year Trial Phase: Endpoints

## A In Full Clinical Remission

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Supportive Care</th>
<th>Supportive Care plus Immunosuppression</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full-analysis set</td>
<td>4/80</td>
<td>14/82</td>
<td>4.82 (1.43–16.30)</td>
<td>0.01</td>
</tr>
<tr>
<td>Available-case analysis</td>
<td>4/72</td>
<td>14/71</td>
<td>5.38 (1.55–18.66)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

## B eGFR Decrease ≥15 ml/min/1.73 m²

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Supportive Care</th>
<th>Supportive Care plus Immunosuppression</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full-analysis set</td>
<td>22/80</td>
<td>21/82</td>
<td>0.89 (0.44–1.81)</td>
<td>0.75</td>
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<tr>
<td>Available-case analysis</td>
<td>18/76</td>
<td>17/78</td>
<td>0.89 (0.41–1.90)</td>
<td>0.76</td>
</tr>
</tbody>
</table>

*Figure 2. Primary End Points.*
Post-hoc sub-group analysis of STOP-IgAN

**A**  
In Full Clinical Remission

<table>
<thead>
<tr>
<th>subgroup</th>
<th>no. of events/total no.</th>
<th>odds ratio (97.5% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>high-GFR</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>
</tr>
<tr>
<td>Corticosteroid Monotherapy</td>
<td>3/51</td>
<td>11/47</td>
<td>5.38 (1.1-26.28)</td>
</tr>
<tr>
<td>low-GFR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supportive Care</td>
<td>1/26</td>
<td>3/27</td>
<td>3.58 (0.26-55.89)</td>
</tr>
<tr>
<td>Immunosuppressive Combination Therapy</td>
<td>1/21</td>
<td>3/24</td>
<td>2.24 (0.16-30.72)</td>
</tr>
</tbody>
</table>

**B**  
GFR Decrease at least 15 ml/min/1.73 m²

<table>
<thead>
<tr>
<th>subgroup</th>
<th>no. of events/total no.</th>
<th>odds ratio (97.5% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>high-GFR</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>
</tr>
<tr>
<td>Corticosteroid Monotherapy</td>
<td>14/52</td>
<td>10/53</td>
<td>0.62 (0.22-1.8)</td>
</tr>
<tr>
<td>low-GFR</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>
</tr>
<tr>
<td>Immunosuppressive Combination Therapy</td>
<td>4/24</td>
<td>7/25</td>
<td>1.79 (0.37-8.64)</td>
</tr>
</tbody>
</table>

### 3-Year Trial Phase: Key Safety Data

<table>
<thead>
<tr>
<th></th>
<th>SUP (n=80)</th>
<th>IMM (n=82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with at least one SAE</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>Total number of SAEs</td>
<td>27</td>
<td>30</td>
</tr>
<tr>
<td>Total number of infectious events</td>
<td>111</td>
<td>182</td>
</tr>
<tr>
<td>Total number of infectious SAEs</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Death</td>
<td>1 (accident)</td>
<td>1 (sepsis)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Impaired glucose tolerance / diabetes</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Body weight gain (≥ 5 kg in the first year)</td>
<td>5</td>
<td>14</td>
</tr>
</tbody>
</table>
Summary & Conclusions

- The addition of immunosuppressive therapy to intensive supportive care in patients with high-risk IgA nephropathy did not significantly improve the outcome.

- Immunosuppression did not affect GFR loss at 3 years, induced only a transient reduction in proteinuria above supportive care.

- More adverse effects were observed among the patients who received immunosuppressive therapy, with no change in the rate of decrease in eGFR.

- In post-hoc sub-group analysis, patients with higher eGFR (>60 ml/min) were more likely to achieve full clinical remission under corticosteroid monotherapy than supportive care, whereas patients with lower eGFR (30-59 ml/min), eGFR-loss rates did not differ between treatment regimens.

STOP-IgAN. NEJM 2015; J Am Soc Nephrol 29:, 2017
Investigator-initiated, international, randomized, double-blind, placebo-controlled trial

IgA nephropathy at high risk of progression:
eGFR 20-120 mls/min/1.73 m²;
Proteinuria >1g/day after at least 3 months of maximum labelled or tolerated RAS blockade

Similar regimen as suggested by the KDIGO guidelines for IgA nephropathy

Trial profile

523 patients screened

262 randomized

261 (50%) excluded during run-in phase:
- 31 (12%) estimated GFR <20 or >120 ml/min/1.73 m²
- 128 (49%) proteinuria <1 g/day
- 3 (1%) HBsAG +ve
- 74 (28%) participant decision
- 25 (10%) other reasons

136 assigned to methylprednisolone

2 lost follow-up

134 primary outcome available

126 assigned to placebo

0 lost follow-up

126 primary outcome available

From May 2012 to November 2015

ZH1

KDIGO
In the primary analysis, everyone randomised contributes so not sure

Hong Zhang, 2019/10/24
Effect on Proteinuria

Time averaged proteinuria: 1.37 vs 2.36 g/day (42% lower)  
P<0.001

<table>
<thead>
<tr>
<th>Month</th>
<th>Mean Δ</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>-0.83</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>6</td>
<td>-1.00</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>12</td>
<td>-1.20</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>24</td>
<td>-1.03</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>36</td>
<td>-0.93</td>
<td>0.0077</td>
</tr>
</tbody>
</table>

Number of patients:

<table>
<thead>
<tr>
<th>Methylprednisolone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>135</td>
<td>123</td>
</tr>
<tr>
<td>117</td>
<td>109</td>
</tr>
<tr>
<td>103</td>
<td>99</td>
</tr>
<tr>
<td>93</td>
<td>88</td>
</tr>
<tr>
<td>55</td>
<td>55</td>
</tr>
<tr>
<td>23</td>
<td>23</td>
</tr>
</tbody>
</table>
Effect on eGFR

Annual eGFR slope*: -1.7 vs -6.8 mls/min/1.73m²/yr  
P=0.031

- defined for each individual patient using the slope from least squares linear regression of all eGFR estimates over time
Primary outcome

composite of ESKD, renal death or 40% decrease in eGFR

HR 0.37 (0.17-0.85)
p = 0.019
Serious adverse events

Hazard ratio 4.95
(95% CI 1.87-17.0), p=0.003
## Safety outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Methylprednisolone group (N=136)</th>
<th>Placebo group (N=126)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients with serious adverse events – no.</td>
<td>20</td>
<td>4</td>
<td>0.001</td>
</tr>
<tr>
<td>Serious adverse events of infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal infection</td>
<td>2</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Pneumocystis jirovecii pneumonia</td>
<td>3</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Other lung infection</td>
<td>2</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Septic arthritis</td>
<td>1</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Perianal infection</td>
<td>1</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Gastrointestinal serious adverse events</td>
<td>3</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Bone disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avascular necrosis</td>
<td>3</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Fracture</td>
<td>1</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>New onset diabetes mellitus</td>
<td>2</td>
<td>3</td>
<td>NS</td>
</tr>
</tbody>
</table>
Full dose steroid therapy was associated with significantly increased rates of serious adverse outcomes in patients with IgA nephropathy.

Although the results are consistent with potential renal benefit, the ongoing, long-term follow-up will help to further define the balance of risks and benefits.

Safer treatment options for IgA nephropathy are required.
## TESTING vs. STOP-IgAN

<table>
<thead>
<tr>
<th></th>
<th>TESTING study</th>
<th>STOP-IgAN</th>
<th>Meta-analysis of prior trials</th>
</tr>
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<tbody>
<tr>
<td><strong>Sample size</strong></td>
<td>262</td>
<td>162</td>
<td>488</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td>Asian 96.3%</td>
<td>Caucasian</td>
<td>Asian 42%</td>
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<tr>
<td></td>
<td>Caucasian 3.7%</td>
<td></td>
<td>Caucasian 58%</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>38.6</td>
<td>44.5</td>
<td></td>
</tr>
<tr>
<td><strong>Female (%)</strong></td>
<td>36.7%</td>
<td>21.5%</td>
<td></td>
</tr>
<tr>
<td><strong>Blood pressure (mmHg)</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>systolic</td>
<td>124.1</td>
<td>125.5</td>
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</tr>
<tr>
<td>diastolic</td>
<td>79.5</td>
<td>77.5</td>
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</tr>
<tr>
<td><strong>Proteinuria (g/d)</strong></td>
<td>2.4</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td><strong>eGFR (ml/min/1.73m²)</strong></td>
<td>59</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td><strong>Annual eGFR decline in supportive group</strong></td>
<td>-6.8</td>
<td>-1.6</td>
<td></td>
</tr>
<tr>
<td><strong>Annual eGFR decline in Steroids group</strong></td>
<td>-1.7</td>
<td>-1.5</td>
<td></td>
</tr>
<tr>
<td><strong>RR for Kidney failure</strong></td>
<td>0.36 (0.16 to 0.82)</td>
<td>NA</td>
<td>0.32 (0.15 to 0.67)</td>
</tr>
</tbody>
</table>
# TESTING vs. STOP-IgAN

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Baseline UP (g/d)</th>
<th>Baseline GFR a</th>
<th>FU</th>
<th>GFR Slope b</th>
<th>Effect HR/OR</th>
<th>Serious infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>TESTING Study</td>
<td>262</td>
<td>2.4</td>
<td>59.3</td>
<td>2.1yr</td>
<td>-1.7 vs -6.8</td>
<td>0.37 (0.17–0.85)</td>
<td>8.1% vs 0%</td>
</tr>
<tr>
<td>Asian</td>
<td>96.3%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STOP-IgAN Caucasian</td>
<td>162</td>
<td>2.2</td>
<td>59.0</td>
<td>3yr</td>
<td>-1.4 vs -1.6</td>
<td>0.97 (0.29–3.22)</td>
<td>9.7% vs 3.8%</td>
</tr>
</tbody>
</table>

a Baseline GFR: ml/min/1.73m²
b GFR Slope: ml/min/1.73m²/yr
TESTING Low Dose Study

Oral methylprednisolone 0.4mg/kg/day initially, maximal dose of 32mg/day, minimum dose of 24mg/day and then reducing over 6-9 months vs. Placebo

Prophylactic trimethoprim/sulfamethoxazole for the first 3 months

China(18), Australia(3), Canada(8), India(6) and Malaysia(6)

2017.5 initiated

2019.10 completed the randomization (240)
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

- Targeted local delivery of potent immunosuppressive agent budesonide to Peyer’s patches in the ileum
- 90% first pass liver metabolism minimize systemic side effects; significantly reduced development risk

Lancet. Published online March 28, 2017
NEFIGAN Trial: Design

RUN-IN PHASE
6 months

Optimize RAS Blockade*

Main Inclusion criteria:
• ≥18 years
• Biopsy-verified IgAN
• UPCR ≥0.5 g/g OR
  Urine protein ≥0.75 g/day
• eGFR ≥45 mL/min/1.73m²

TREATMENT PHASE
9 months

NEFECON 16 mg/day

NEFECON 8 mg/day

PLACEBO

FOLLOW-UP PHASE
3 months

2 week tapering at 8 mg/day

2 week placebo tapering

2 week placebo tapering

*Optimized RAS Blockade throughout Treatment and Follow-up Phases

Primary Outcome
Change from baseline in UPCR

150 IgAN Patients
Time Frame: 9 months

KDIGO
The NEFIGAN Trial

NEFECON Time-dependent reduction in UPCR

NEFECON stabilized eGFR*

Lancet. March 28, 2017
Summary & Conclusions

NEFECON treatment
- Significantly reduced UPCR
- Stabilized eGFR
- Was generally well-tolerated, consistent with low systemic exposure

TRF budesonide represents an attractive novel, pathophysiology-based approach to IgAN. Disease modifying by suppression of production or leakage of the aberrant IgA antibody into the circulation. It may offer a new and comparatively safe option to treat patients at risk for progressive IgAN.
The NEFIGARD Trial

ClinicalTrials.gov Identifier: NCT03643965

<table>
<thead>
<tr>
<th>Study Design</th>
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</thead>
<tbody>
<tr>
<td><strong>Study Type</strong>: Interventional (Clinical Trial)</td>
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<tr>
<td><strong>Estimated Enrollment</strong>: 450 participants</td>
</tr>
<tr>
<td><strong>Allocation</strong>: Randomized</td>
</tr>
<tr>
<td><strong>Intervention Model</strong>: Parallel Assignment</td>
</tr>
<tr>
<td><strong>Masking</strong>: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)</td>
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<tr>
<td><strong>Primary Purpose</strong>: Treatment</td>
</tr>
<tr>
<td><strong>Official Title</strong>: A Randomized, Double-blind, Placebo Controlled Study to Evaluate Efficacy and Safety of Nefecon in Patients With Primary IgA (Immunoglobulin A) Nephropathy at Risk of Progressing to End-stage Renal Disease (NeflgArd)</td>
</tr>
<tr>
<td><strong>Actual Study Start Date</strong>: September 5, 2018</td>
</tr>
<tr>
<td><strong>Estimated Primary Completion Date</strong>: October 2020</td>
</tr>
<tr>
<td><strong>Estimated Study Completion Date</strong>: December 2024</td>
</tr>
</tbody>
</table>

- **Sponsor**: Calliditas Therapeutics AB
- **CRO**: Medpace
- **Investigational Product**: Nefecon
- **Study Phase**: III
- **Estimated Enrollment**: 450 participants (146 Sites in 19 Countries/Districts currently)

*China will join soon!*
KDIGO did suggest the use corticosteroids in selected patients with IgAN, particularly when the supportive care was optimized.

STOP-IgAN and TESTING study have provided important insights into the value of steroid therapy in IgAN

- The efficacy of steroids in the protection for future renal function decline in IgAN is considerable debate
- Both studies have shown that the steroids significantly increased risk of serious adverse events, particularly serious infections.

With the available evidence, the treatment of IgAN with corticosteroids should likely be limited to patients at highest risk of disease progression who understand and accept the significant risk of adverse events.
Controlled Prospective Trial of Prednisolone and CTX in Progressive IgA Nephropathy

Francis W. Ballardie, and Ian S. D. Roberts JASN 2002;13:142-148
Addition of Azathioprine to Corticosteroids Does Not Benefit Patients with IgA Nephropathy

Claudio Pozzi et al. JASN 2010;21:1783-1790
<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Sample size</th>
<th>Treatment</th>
<th>Control</th>
<th>Follow-up</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen 2002</td>
<td>UPE &gt; 2.0 g/d, Scr &lt; 4 mg/dL Lee III-IV</td>
<td>62 (31/31)</td>
<td>MMF, 1.5 g/d 1.0-0.75 g/d</td>
<td>Prednisone</td>
<td>18 M</td>
<td>Clinical remission SAE</td>
</tr>
<tr>
<td>Maes 2004</td>
<td>UPE &gt; 1.0 g/d, GFR 20-70 ml/min excluded rapidly progressive IgAN</td>
<td>34 (21/13)</td>
<td>MMF, 2g/day</td>
<td>Placebo</td>
<td>36 M</td>
<td>Kidney survival Proteinuria BP</td>
</tr>
<tr>
<td>Frisch 2005</td>
<td>UPE &gt; 1.0 g/d, GFR 20-70 ml/min excluded &gt;50% active crescents</td>
<td>32 (17/15)</td>
<td>MMF, 2g/day RASi</td>
<td>RASi</td>
<td>24 M</td>
<td>Clinical remission eGFR, ESRD, SAE</td>
</tr>
<tr>
<td>Tang 2010</td>
<td>Proteinuria &gt; 1.0 g/d, Scr &lt; 300 umol/L Excluded Haas 1 and 5</td>
<td>40 (20/20)</td>
<td>MMF, 2-1.5 g/d for 6 months</td>
<td>RASi</td>
<td>18 M</td>
<td>Proteinuria Reduction by 30%, renal survival benefit</td>
</tr>
<tr>
<td>Hogg 2015</td>
<td>UPCR ≥ 0.6 g/g (male) or ≥ 0.8 g/g(female) eGFR ≥50 mL/min</td>
<td>44 (22/22)</td>
<td>MMF (25-36 mg/kg, max 2.0 g/d)</td>
<td>Placebo</td>
<td>6 M</td>
<td>Complete remission (UPCR, 0.2 g/g)</td>
</tr>
<tr>
<td>Hou 2017</td>
<td>UPE ≥ 1.0 g/d, eGFR&gt; 30 mL/min 10%-50% C, E, or glomerular necrosis, with &lt;50% T</td>
<td>174 (86/88)</td>
<td>MMF, 1.5 g/d, Prednisone, 0.4-0.6mg/kg/d. for 6 months</td>
<td>Prednisone 0.8-1.0mg/kg/d for 6 months</td>
<td>6 M</td>
<td>Complete remission ESRD, Scr doubling SAE</td>
</tr>
</tbody>
</table>
Summary: MMF in IgAN

Efficacy of MMF Remains Controversial

- The study population is limited
- The study quality is low
- The study inclusion is variable
- The study based on histopathology is rare
Corticosteroids in IgAN

uncertain benefit of corticosteroids in those with low eGFR, in different ethnic groups; it was addressed that usage of corticosteroids needs to balance risks and benefits

There is still insufficient evidence for other immunosuppressive therapy in IgAN

However, with the available evidence

**MMF might be a valid option, especially**

- For patients in Asians (Chinese);
- For patients histologically with “active” lesions;
- For patients at risk of progression
- For steroid-sparing regimen

---

Corticosteroids in IgAN

Uncertain benefit of corticosteroids in those with low eGFR, in different ethnic groups; it was addressed that usage of corticosteroids needs to balance risks and benefits.

There is still insufficient evidence for other immunosuppressive therapy in IgAN.

However, with the available evidence, **MMF might be a valid option, especially**:

- For patients in Asians (Chinese);
- For patients histologically with “active” lesions;
- For patients at risk of progression;
- For steroid-sparing regimen.

---

Table S1. 2012 KDIGO GN guideline recommendations related to IgA nephropathy: Need to be revisited?

<table>
<thead>
<tr>
<th>Guideline recommendations</th>
<th>Need to be revisited?</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.1: Initial evaluation including assessment of risk of progressive kidney disease</td>
<td>Yes^1^, ^6^</td>
</tr>
<tr>
<td>10.1.2: Assess the risk of progression in all cases by evaluation of proteinuria, blood pressure, and eGFR at the time of diagnosis and during follow-up. (Not Graded)</td>
<td></td>
</tr>
<tr>
<td>10.1.3: Pathological features may be used to assess prognosis. (Not Graded)</td>
<td></td>
</tr>
<tr>
<td>10.3: Corticosteroids</td>
<td>Yes^7^–^10^</td>
</tr>
<tr>
<td>10.3.1: We suggest that patients with persistent proteinuria $\geq$ 1 g/d, despite 3–6 months of optimized supportive care (including ACE-I or ARBs and blood pressure control), and GFR $&gt; 50$ ml/min per 1.73 m², receive a 6-month course of corticosteroid therapy. (2C)</td>
<td></td>
</tr>
<tr>
<td>10.4: Immunosuppressive agents</td>
<td></td>
</tr>
<tr>
<td>10.4.1: We suggest not treating with corticosteroids combined with cyclophosphamide or azathioprine in IgAN patients (unless there is crescentic IgAN with rapidly deteriorating kidney function; see Recommendation 10.6.3). (2D)</td>
<td></td>
</tr>
<tr>
<td>10.4.2: We suggest not using immunosuppressive therapy in patients with GFR $&lt; 30$ ml/min per 1.73 m² unless there is crescentic IgAN with rapidly deteriorating kidney function (see Section 10.6). (2C)</td>
<td></td>
</tr>
<tr>
<td>10.4.3: We suggest not using MMF in IgAN. (2C)</td>
<td>Yes^13^, ^14^</td>
</tr>
<tr>
<td>10.5: Other treatments</td>
<td></td>
</tr>
<tr>
<td>10.5.3: We suggest that tonsillectomy not be performed for IgAN. (2C)</td>
<td>No^15^, ^16^</td>
</tr>
</tbody>
</table>

eGFR, estimated glomerular filtration rate; IgAN, IgA nephropathy

There are gaps in recommendations above since not all of the 2012 KDIGO guideline statements were reviewed or evaluated at the conference.
Pathogenesis: The ‘multi-hit’ hypothesis

Mucosal & innate immunity
- Dysregulated response to mucosal antigens
  - HORMAD2, DEFA, TNFSF13, LIF/OSM, CARD9, ITGAM - ITGAX, VAV3,

Adaptive immunity
- Defect in allore cognition
  - MHC alleles

Alternative complement pathway
- Tissue inflammation, immune complex clearance
  - CFHR1 and CFHR3, ITGAM - ITGAX

GWAS identified susceptibility gene loci involved in IgA nephropathy, which provide new insights for treatment options

Adapted from Kidney Int. 2015;88(5):974-89.
<table>
<thead>
<tr>
<th>Row</th>
<th>Status</th>
<th>Study Title</th>
<th>Interventions</th>
<th>Study Design</th>
<th>Number Enrolled</th>
<th>NCT Number</th>
<th>Last Update Posted</th>
<th>Locations</th>
</tr>
</thead>
</table>
| 1   | Not yet recruiting | Study of Safety and Efficacy of AVB-S6-500 in Patients With IgA Nephropathy | Drug: AVB-S6-500                                                               | Intervention Model: Single Group Assignment  
• Masking: None (Open Label)  
• Primary Purpose: Treatment | 12             | NCT04042623                  | August 2, 2019          | United States, Colorado Kidney Care, Denver, Colorado, United States |
| 2   | Not yet recruiting | A Study to Evaluate the Effectiveness and Safety of IONIS-FB-LRx, an Antiinflammatory Inhibitor of Complement Factor B, in Adult Participants With Primary IgA Nephropathy | Drug: IONIS-FB-LRx                                                             | Intervention Model: Single Group Assignment  
• Masking: None (Open Label)  
• Primary Purpose: Treatment | 10             | NCT04014335                  | August 8, 2019         | United States, United Kingdom |
| 3   | Recruiting       | A Study of Cemdisiran in Adults With IgA Nephropathy (IgAN)                | Drug: BION-1301 SGL  
Drug: Placebo Single Dose  
Drug: BION-1301 Multiple Doses  
Drug: Placebo Multiple Doses | Allocation: Randomized  
Intervention Model: Parallel Assignment  
• Masking: Triple (Participant, Care Provider, Investigator)  
• Primary Purpose: Treatment | 73             | NCT03945318                  | May 10, 2019          | United States, United Kingdom |
| 4   | Recruiting       | A Study of Cemdisiran in Adults With IgA Nephropathy (IgAN)                | Drug: Placebo  
Drug: Cemdisiran                                                                 | Allocation: Randomized  
Intervention Model: Parallel Assignment  
• Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)  
• Primary Purpose: Treatment | 30             | NCT03841448                  | August 12, 2019        | United States, Clinical Trial Site Lynwood, California, United States |
| 5   | Recruiting       | First in Human Study to Assess Safety of VIS649 in Healthy Subjects         | Biological: VIS649  
Biological: Placebo                                                              | Allocation: Randomized  
Intervention Model: Parallel Assignment  
• Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)  
• Primary Purpose: Treatment | 45             | NCT03719443                  | February 27, 2019       | United States, California Clinical Trials Medical Group United States |
| 6   | Recruiting       | Efficacy and Safety of Nefecon in Patients With Primary IgA (Immunoglobulin A) Nephropathy | Drug: Nefecon  
Drug: Placebo oral capsule                                                      | Allocation: Randomized  
Intervention Model: Parallel Assignment  
• Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)  
• Primary Purpose: Treatment | 450            | NCT03643965                  | May 17, 2019          | United States, University of Alabama at Birmingham, Alabama, United States |
| 7   | Recruiting       | Fecal Microbiota Transplantation for Refractory IgA Nephropathy             | Biological: Fecal microbiota transplantation                                  | Intervention Model: Single Group Assignment  
• Masking: None (Open Label)  
• Primary Purpose: Treatment | 30             | NCT03633864                  | August 21, 2018        | China, Xi`an, Shaanxi, Xijing Hospital of Nephrology |
| 8   | Recruiting       | Study of the Safety and Efficacy of OMS721 in Patients With Immunoglobulin A (IgA) Nephropathy | Biological: OMS721  
Other: Vehicle (DSW or saline)                                                   | Allocation: Randomized  
Intervention Model: Parallel Assignment  
• Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)  
• Primary Purpose: Treatment | 450            | NCT03608033                  | May 30, 2019          | United States, Omeros Investigational Site, Florence, Alabama, United States |
| 9   | Recruiting       | Phase II Study Assessing Safety and Efficacy of APL-2 in Glomerulopathies   | Drug: APL-2                                                                  | Intervention Model: Single Group Assignment  
• Masking: None (Open Label)  
• Primary Purpose: Treatment | 48             | NCT03453619                  | January 15, 2019       | United States, Apellis Investigational Site United States |
| 10  | Recruiting       | Study of Safety and Efficacy of LNP023 in Patients With Kidney Disease Caused by Inflammation | Drug: LNP023  
Drug: Placebo                                                                | Allocation: Randomized  
Intervention Model: Parallel Assignment  
• Masking: Double (Participant, Investigator)  
• Primary Purpose: Treatment | 118            | NCT03373461                  | May 24, 2019          | Argentina, Novartis Investigational Site Buenos Aires, Argentina |
### IgA Nephrology Clinical Trials

<table>
<thead>
<tr>
<th>Row</th>
<th>Status</th>
<th>Study Title</th>
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<th>Number Enrolled</th>
<th>NCT Number</th>
<th>Last Update Posted</th>
<th>Locations</th>
</tr>
</thead>
</table>
| 11  | Active, not recruiting | Efficacy and Safety of Atacicept in IgA Nephropathy | - Drug: Atacicept 25 mg  
- Drug: Atacicept 75 mg  
- Drug: Atacicept 150 mg  
- Drug: Placebo | Allocation: Randomized  
- Intervention Model: Parallel Assignment  
- Masking: Double (Participant, Investigator)  
- Primary Purpose: Treatment | 30  | NCT02808429  | October 26, 2018  | Research site Glendale, Arizona, United States |
| 12  | Active, not recruiting | Prevention in Recipients With Primary IgA Nephropathy of Recurrence After Kidney Transplantation: ATG-F Versus Basiliximab as Induction Imunosuppressive Treatment | - Drug: ATG-F  
- Drug: Simulect | Allocation: Randomized  
- Intervention Model: Parallel Assignment  
- Masking: None (Open Label)  
- Primary Purpose: Treatment | 115  | NCT02523768  | December 20, 2018  | CHU de BESANCON Besancon, France |
| 13  | Completed  | Open-Label Study to Evaluate Safety and Efficacy of CCX168 in Subjects With Immunoglobulin A Nephropathy on Stable RAAS Blockade | - Drug: CCX168 | Intervention Model: Single Group Assignment  
- Masking: None (Open Label)  
- Primary Purpose: Treatment | 5  | NCT02384317  | May 29, 2019  | Palo Alto, California, United States |
| 14  | Completed Has Results | Pilot Study of ACTH in the Treatment of Immunoglobulin A (IgA) Nephropathy at High Risk of Progression | - Drug: ACTH (Acthar) Gel | Intervention Model: Single Group Assignment  
- Masking: None (Open Label)  
- Primary Purpose: Treatment | 20  | NCT02282930  | June 26, 2019  | Stanford University California, United States |
| 15  | Completed Has Results | Safety and Efficacy Study of Fostamatinib to Treat Immunoglobulin A (IgA) Nephropathy | - Drug: Fostamatinib 150 mg  
- Drug: Fostamatinib 100 mg  
- Drug: Placebo | Allocation: Randomized  
- Intervention Model: Parallel Assignment  
- Masking: None (Open Label)  
- Primary Purpose: Treatment | 76  | NCT02112838  | June 27, 2019  | Stanford University California, United States |
| 16  | Completed  | BRIGHT-SC: Blisibimod Response in IgA Nephropathy Following At-Home Treatment by Subcutaneous Administration | - Drug: Blisibimod  
- Drug: Placebo | Allocation: Randomized  
- Intervention Model: Parallel Assignment  
- Masking: None (Open Label)  
- Primary Purpose: Treatment | 57  | NCT02062684  | September 18, 2017  | Investigator Site 852 Olomouc, Czechia |
| 17  | Completed Has Results | Pilot Study of Velcade® in IgA Nephropathy | - Drug: Bortezomib (Velcade®) | Intervention Model: Single Group Assignment  
- Masking: None (Open Label)  
- Primary Purpose: Treatment | 11  | NCT01103778  | November 16, 2018  | The Rogosin Institute New York, New York, United States |
| 18  | Terminated | Safety Study of Intravenous CCL2-LPM in Patients With IgA Nephropathy  
Single核細胞趨化蛋白-1(MCP-1, CCL2) | Biological: OPL-CCL2-LPM | Intervention Model: Single Group Assignment  
- Masking: None (Open Label)  
- Primary Purpose: Treatment | 30  | NCT00856674  | June 2, 2010  | Nephrology Unit Hôpital Nord CHU de Saint-Etienne  
Saint-Etienne, France |
| 19  | Completed  | Role of Regulatory T Cells in Pathogenesis of Primary IgA Nephropathy | Procedure: gene transcription and cytometry | Allocation: Non-Randomized  
- Intervention Model: Parallel Assignment  
- Masking: None (Open Label)  
- Primary Purpose: Diagnostic | 45  | NCT00521508  | September 29, 2010  | Nephrology Department  
Hospital Universitari de Bellvitge  
L’Hospitalet de Llobregat, Barcelona, Spain |
| 20  | Completed  | Sirolimus Therapy for Poor Prognosis Immunoglobulin A Nephropathy  
mTOR蛋白特异性抑制剂 | - Drug: ACE inhibitor + statin  
- Drug: Sirolimus (study drug)  
- Drug: ACE inhibitor + statin | Allocation: Randomized  
- Intervention Model: Parallel Assignment  
- Masking: None (Open Label)  
- Primary Purpose: Treatment | 23  | NCT00396721  | September 16, 2011  | Nephrology Unit Hôpital Nord CHU de Saint-Etienne  
Saint-Etienne, France |
Proposed pathogenesis of IgA nephropathy and potential therapeutic targets.

- Enteric corticosteroids
- Rituximab
- Blisibimod, Atacicept
- Fostamatinib (Syk-BCR)
- Bortezomib
- Eculizumab and OMS721

Complement FB inhibitor

Management and treatment of GN: a KDIGO conference report
Kidney International (2019) 95, 268–280
Treatment of IgA nephropathy

What have we learn from recent RCTs?

- RASB remains to be the first-line therapy
- Usage of corticosteroids needs to balance risks and benefits
- There is still insufficient evidence for other immunosuppressant in IgAN
- Targeting pathogenic pathway, including mucosal immunity, B-cell activation, complement activation, and proteasome pathway, is promising in the future
- With better understanding of pathogenesis of IgAN, emerging therapies will soon become a reality in the coming year
Acknowledgments
Acknowledgments

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Peking University Health Central Clinical Research Project (PUCRP201102)
Pfizer Pharmaceuticals (study drug supply)
Canadian Institutes of Health Research

Endorsement
Australasian Kidney Trials Network

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