IgA Nephropathy

- In IgA nephropathy, which of the following clinical syndromes has the best long-term outcome?
  A. Episodic macroscopic hematuria
  B. Persistent microscopic hematuria
  C. Microscopic hematuria and 3 grams of proteinuria
  D. Episodic microscopic hematuria and persistent hematuria

Patients with Various Glomerular Diseases and Crescent Formation

<table>
<thead>
<tr>
<th>Disease</th>
<th>% with Crescent</th>
<th>Avg Glomeruli with Crescent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-GBM antibody-mediated GN</td>
<td>95</td>
<td>17</td>
</tr>
<tr>
<td>ANCA-associated GN</td>
<td>90</td>
<td>48</td>
</tr>
<tr>
<td>Immune complex-mediated GN</td>
<td>50</td>
<td>48</td>
</tr>
<tr>
<td>Lupus GN (class II and IV)</td>
<td>40</td>
<td>11</td>
</tr>
<tr>
<td>HSP</td>
<td>53</td>
<td>5</td>
</tr>
<tr>
<td>IgA nephropathy</td>
<td>27</td>
<td>24</td>
</tr>
<tr>
<td>Acute postinfectious GN</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>Fibrillary GN</td>
<td>20</td>
<td>7</td>
</tr>
<tr>
<td>Type I membranoproliferative GN</td>
<td>20</td>
<td>3</td>
</tr>
<tr>
<td>Membranous lupus GN (class V)</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Membranous GN (non-lupus)</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

Demographics of IgA Nephropathy

IgA nephropathy is the most common glomerulonephritis in the world. In native kidney biopsies, IgA nephropathy accounts for:

<table>
<thead>
<tr>
<th></th>
<th>All biopsies (%)</th>
<th>GN biopsies (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Asia</td>
<td>30</td>
<td>40</td>
</tr>
<tr>
<td>Europe</td>
<td>15</td>
<td>20</td>
</tr>
</tbody>
</table>

Rare in African Americans; common in Native Americans. Even with low progression rate, high prevalence results in 10-20% contribution to ESRD.

GWAS-Identified Loci for IgAN

- Adaptive immunity
  » 3 loci on chromosome 6p21 in the MHC region
- Innate immunity
  » 8p23 DEFA locus
  » 17p23 TNFSF13 locus
  » 22q12 HORMAD2 locus
- Alternative complement pathway
  » 1q32 CFH/CFHR locus
Ethnic Differences in Prevalence of IgAN in the US

IgA Nephropathy is Morphologically Heterogeneous

Light Microscopic Morphology

Normal Glomeruli → Mesangial Proliferative Glomerulopathy

Asymptomatic Hematuria/Proteinuria → Proliferative Glomerulonephritis

Chronic Glomerulonephritis → End Stage Kidney

Chronic Nephritis

Rapidly Progressive Nephritis → End Stage Kidney

Structure of Human IgA1

IgA1 Hinge Region

Oxford Classification of IgA Nephropathy

- Working Group of the International IgA Nephropathy Network and the Renal Pathology Society
- Six pathologic variables identified that could be used to interrogate prognostic significance independent of the clinical data in IgA nephropathy:
  1. Mesangial cellularity score; percentage of glomeruli showing
  2. Segmental sclerosis
  3. Endocapillary hypercellularity
  4. Cellular/fibrocellular crescents
  5. Percentage of interstitial fibrosis/tubular atrophy
  6. Arteriosclerosis score
Proposed Multi-Hit Mechanism in IgA Pathogenesis

- **Hit #1**: Synthesis of galactose-deficient IgA1 by a sub-population of IgA1-secreting cells.
- **Hit #2**: Formation of autoantibodies with characteristics of the variable region of the heavy chain that recognize galactose-deficient IgA1.
- **Hit #3**: Formation of pathogenic immune complexes from auto-antigen (galactose-deficient IgA1) and auto-antibody (anti-glycan IgG or IgA1).
- **Hit #4**: Immune complexes activate mesangial cells to proliferate and secrete a wide variety of growth factors and cytokines that cause renal injury.

**Induction of Glomerular and Tubulointerstitial Injury by Pathogenic IgA1-Containing Immune Complexes**

**Clinical patterns of IgA presentation are fair game for Board exams**

- **Episodic macroscopic hematuria**
  - Most frequent in children
  - Associated with respiratory or GI tract infection; flank or loin pain common
  - Nephrotic syndrome and hypertension uncommon
  - Prolonged remissions of clinical signs

- **Asymptomatic hematuria and proteinuria**
  - Persistent microscopic hematuria
  - Hypertension more common
  - Impairment of renal function may be apparent at presentation
  - Remission uncommon
  - Rapidly progressive glomerulonephritis
  - Nephrotic syndrome
  - Acute renal failure with gross hematuria

**Predictors of Poor Kidney Outcome**

- **Scr < 120 μmol/L** and **> 120 μmol/L** (p<0.001 log rank test)
- **Hypertension** (diastolic > 95 mm Hg or antihypertensive treatment) (p<0.001 log rank test)
- **Urinary protein excretion < 1 g/24 hr** and **> 1 g/24 hr** (p < 0.025 log rank test)
- **Have stood the test of time**

**Risk Factors for Progression: Clinical-Proteinuria**

- **24-hour urine protein excretion one year after diagnosis** was highly predictive of ESRD within 7 years of subsequent follow-up
Causes of Nephrotic Syndrome

- Advanced glomerular scarring
- Diffuse proliferative glomerulonephritis
- Overlap between IgA nephropathy, minimal change disease, and other glomerular diseases

WHAT ABOUT ACE INHIBITORS OR ARB’s?

Use of:

- ACEi
- ARB
- Aldosterone blockers
  - Generally very useful in lowering proteinuria

ACEi and Prednisone May Be of Benefit


Kidney survival estimated based on an increase up to 50% greater than baseline serum creatinine level and a decrease of 25% in estimated glomerular filtration rate (eGFR).

ACEI’S ENHANCE EFFECTS OF POLYUNSATURATED FATS
**WHAT ABOUT CORTICOSTEROIDS?**

**Corticosteroids in IgA Nephropathy**
- 6-month course of steroid treatment
- Either supportive therapy or steroid treatment (IV methylprednisolone); on months 1, 3, and 5 with oral glucocorticoid therapy

**Prednisone and Cytotoxics in IgA Nephropathy**
- 38 patients with progressive IgA nephropathy
- Randomized to treatment with prednisone, low-dose cyclophosphamide then azathioprine, and to supportive care

**Risk factors**
- Vascular sclerosis
  - Relative risk for 1-point increase in score 1.53, p=0.0347
- Female sex (0.22, p=0.163)
- Steroid therapy (0.41, p=0.0439)
Renal Survival Estimated on Increase in Plasma Creatinine Concentrations to > 100% Above Baseline

WHAT ABOUT FISH OIL?

Fish Oil Therapy for IgA Nephropathy

- Meta-analysis
- 5 controlled studies
- Mean effect of fish oil not statistically significant
- Probability of a minor beneficial effect was 75%

Cumulative % of IgA Patients Treated with Fish Oil or Placebo with ESRD or Died During or After 2-Yr Treatment Period

The Tonsils in IgAN

- Tonsillectomy in IgA is a practice in Asia, and is controversial
- Tonsillectomy possibly decreases hematuria and proteinuria (effect on ESRD)

Update

MMF THERAPY IN IGA IS CONTROVERSIAL. IF YOU ARE GOING TO USE IT IN PRACTICE, USE IT EARLY.
Update

Multicenter study in 18 university or community hospitals located in major cities in Japan between 04/01/2005-03/31/2010

Participating institutions routinely performed tonsillectomy combined with steroid pulses to treat IgAN

Conclusions:
- No beneficial effect over steroid pulse therapy alone to attenuate hematuria or to increase the incidence of clinical remission
- Antiproteinuric effect was significantly greater in combined therapy, but the difference was marginal and impact on renal function remains to be clarified

Crescentic IgA Nephropathy

N=12 with crescentic, proliferative IgA
Pulse Solu-Medrol x 3 days, then monthly IV cyclophosphamide x 6 months
On repeat kidney biopsy, elimination of endocapillary proliferation, cellular crescents and karyorrhexis in all patients after 6 months

Treatment According to KDIGO Guidelines

Recommendation
- ACE-I or ARB for urinary protein excretion of > 1 g/day; ↑ dose depending on BP

Suggestions
- Proteinuria
  - ACE-I or ARB if urinary protein excretion of 0.5-1.0 g/day; ↑ dose if adverse events are acceptable to achieve urinary protein excretion of < 1 g/day
  - 6-mo glucocorticoid therapy if proteinuria ≥ 1 g/day continues after 3 mos
  - Fish oil or proteinuria > 1 g/day continues after 3 to 6 mos
- Blood Pressure
  - < 130/80 mm Hg if proteinuria is < 1 g/day, but < 125/75 mm Hg if initial proteinuria is > 1 g/day
- Rapidly Declining eGFR
  - Glucocorticoids + cyclophosphamide for crescentic IgA (>50% glomeruli with crescents) with rapid deterioration of eGFR
  - Supportive care if kidney biopsy shows acute tubular injury and intratubular erythrocytosis

Synopsis of Suggested Therapeutic Approaches Based on the Clinical Setting

- Multicenter study in 18 university or community hospitals located in major cities in Japan between 04/01/2005-03/31/2010
- Participating institutions routinely performed tonsillectomy combined with steroid pulses to treat IgAN
- Conclusions:
  - No beneficial effect over steroid pulse therapy alone to attenuate hematuria or to increase the incidence of clinical remission
  - Antiproteinuric effect was significantly greater in combined therapy, but the difference was marginal and impact on renal function remains to be clarified

- Very little data
- I treat with pulse Solu-Medrol (7 mg/kg x 3 days) and IV cyclophosphamide
- But I could be very wrong

Treatment According to KDIGO Guidelines

Recommendation
- ACE-I or ARB for urinary protein excretion of > 1 g/day; ↑ dose depending on BP

Suggestions
- Proteinuria
  - ACE-I or ARB if urinary protein excretion of 0.5-1.0 g/day; ↑ dose if adverse events are acceptable to achieve urinary protein excretion of < 1 g/day
  - 6-mo glucocorticoid therapy if proteinuria ≥ 1 g/day continues after 3 mos
  - Fish oil or proteinuria > 1 g/day continues after 3 to 6 mos
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Synopsis of Suggested Therapeutic Approaches Based on the Clinical Setting
Approach to Treatment of IgA Nephropathy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Clinical Features</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>BP control &lt; 130/80 mm Hg</td>
<td>Strongly consider ACEI or ARB</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider statin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider tonsillectomy if recurrent tonsillitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+/- fish oils per patient preference</td>
</tr>
</tbody>
</table>

Mild disease
- Normal GFR
- Proteinuria < 500 mg/d
- Benign histology
- Normal BP

- Watchful waiting
- Enrollment into prospective observational studies

Moderate/severe disease
- Proteinuria > 1 g/d or proteinuria 0.5-1 g/d with other features suggesting risk of progression (impaired haemodynamics, hypertension, diabetes mellitus, unexplained renal failure)
- Histologic signs suggesting risk of progression (mesangial hypercellularity, endocapillary proliferation, segmental sclerosis)

- Glucocorticoids x 6 mos (trials showing benefits from steroid-treated patients with relatively preserved GFR and proteinuria > 1 g/d)
- Consider cytotoxics (i.e., cyclophosphamide)
- Enrollment into clinical trials

"Point of no return" Low GFR, typically < 30 ml/min/1.73 m²
- Biopsy with severe global glomerulosclerosis and tubular atrophy/interstitial fibrosis
- No immunosuppression
- Prepare for transplant or renal replacement therapy

Crescentic IgAN
- Rapidly progressive GN
- > 30%-50% cellular or fibrocellular crescents on biopsy

- Pulse + high-dose oral glucocorticoids
- Consider cyclophosphamide

IgAN with minimal change disease
- Sudden-onset nephrotic syndrome
- Mesangial IgA deposits on biopsy without sufficient sclerosis to explain proteinuria

- Glucocorticoids, akin to treatment of minimal change disease

Rituximab versus Standard Therapy for IgA Nephropathy

- Open-label multicenter randomized (1:1) controlled trial
- Primary outcome: complete (<300 mg proteinuria, ≤ 10% ↓ eGFR) or partial (> 50% ↓ proteinuria and ≤ 25% ↓ eGFR) remission at 12 months

Study Principal Investigator: Fernando Fervenza, MD, PhD
Mayo Clinic

Henoch-Schönlein Purpura

Vasculitis with IgA dominant immune deposits affecting small vessels: capillaries, venules, or arterioles.
Typically involves skin, gut and glomeruli, and is associated with arthralgias and arthritis.

Can corticosteroid therapy alter the course of nephritis in children with HSP?

- Prednisone did not reduce incidence of renal symptoms
- Compared with placebo, early prednisone therapy:
  - controlled extrarenal symptoms more effectively
  - reduced the severity of nephritis
  - did not prevent renal involvement

Which of the following statements is most likely correct in patients with anti-GBM disease?

A. This is a disease of people aged less than 40 years
B. There are multiple reactive epitopes
C. It is futile to treat people with a serum creatinine of greater than 300 µmol
D. Immunosuppressive therapy is not needed after 3 to 4 months of therapy
Age Distribution by Gender

![Age Distribution by Gender Graph]

### The Goodpasture Epitope

![Goodpasture Epitope Diagram]

### Therapy

- **Induction**
  - Plasmapheresis
    - 14 daily or alternate-day, 4-liter exchanges
    - Albumin replacement
    - Fresh frozen plasma
    - Pulmonary hemorrhage
    - Recent kidney biopsy
  - Pulse methylprednisolone

- **Maintenance**
  - Prednisone tapering to alternate-day schedule
  - Oral or IV cyclophosphamide
  - Cyclophosphamide 1 mg/kg/day and azathioprine 12 mg/kg/day

### Renal and Patient Survival at 1 Year According to Initial Renal Function

<table>
<thead>
<tr>
<th>Renal function at presentation</th>
<th>Ph. e.</th>
<th>Median creatinine concentration</th>
<th>Median proportion of crescents</th>
<th>1 yr patient survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (n%)</td>
<td>µmol/L (range)</td>
<td>%</td>
<td>At 2 mos</td>
</tr>
<tr>
<td>Creatinine concentration &lt;500 µmol/L</td>
<td>19 (100)</td>
<td>207 (53-470)</td>
<td>28 (6-97)</td>
<td>19 (100)</td>
</tr>
<tr>
<td>Creatinine concentration ≥500 µmol/L</td>
<td>13 (93)</td>
<td>708 (565-885)</td>
<td>55 (38-100)</td>
<td>8 (61)</td>
</tr>
<tr>
<td>Dialysis-dependent</td>
<td>29 (13)</td>
<td>198 (62-106)</td>
<td>26 (90)</td>
<td>3 (13)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>71 (100)</td>
<td>317 (53-650)</td>
<td>55 (37)</td>
<td>29 (41)</td>
</tr>
</tbody>
</table>

1. Renal survival at 2 months was calculated only for patients surviving at 2 months.

### ANCA and Anti-GBM

![ANCA and Anti-GBM Images]
ANCA + anti-GBM Antibodies

- 5% of all ANCA-positive serum samples were also positive for anti-GBM antibodies
- 32% of all anti-GBM-positive samples had detectable ANCA
- Patients positive for both ANCA and anti-GBM antibodies have a poor prognosis when presenting with severe disease
- Behaves like anti-GBM early; relapses like ANCA vasculitic disease

LUPUS NEPHRITIS

Lupus Nephritis

- Which of the following has been shown to be the best remission maintenance therapy?
  A. Glucocorticoids
  B. Rituximab
  C. Cyclophosphamide
  D. Mycophenolate mofetil
  E. Azathioprine

Query

2002 ISN/RPS Consensus Conference on the Classification of Lupus Glomerulonephritis

Class I  Minimal mesangial lupus glomerulonephritis (LGN)
Class II  Mesangial proliferative LGN
Class III  Focal LGN (involving < 50% of glomeruli)
Class IV  Diffuse LGN (involving ≥ 50% glomeruli, IV-S and IV-G)
Class V  Membranous LGN
Class VI  Advanced sclerotic LGN (> 90% sclerotic glomeruli)

Clinical Associations of Autoantibodies in SLE

<table>
<thead>
<tr>
<th>Antigen Specificity</th>
<th>Clinical Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>dsDNA</td>
<td>Marker for active disease; titers fluctuate with disease activity</td>
</tr>
<tr>
<td>ssDNA</td>
<td>Nonspecific</td>
</tr>
<tr>
<td>Ro/SSA</td>
<td>Cutaneous lupus (75%), photosensitivity, neonatal lupus</td>
</tr>
<tr>
<td>La/SSB</td>
<td>With La, low prevalence of renal disease; neonatal lupus (75%)</td>
</tr>
<tr>
<td>Sm</td>
<td>Marker for disease; may be associated with CNS disease</td>
</tr>
<tr>
<td>RNP (U1-RNP)</td>
<td>MCTD, required for diagnosis</td>
</tr>
<tr>
<td>Phospholipids</td>
<td>Hypercoagulable state in some, no significance in others; thrombocytopenia, later trimester abortions</td>
</tr>
<tr>
<td>Histones</td>
<td>&gt;90% in drug-related lupus; present in RA, SLE, systemic sclerosis with pulmonary fibrosis</td>
</tr>
<tr>
<td>Ku</td>
<td>SLE, MCTD (Europeans/Americans), scleroderma/myositis overlap (Japanese)</td>
</tr>
</tbody>
</table>
Renal Survival by Race


Sequential Therapies for Proliferative Lupus Nephritis

- Induction therapy of 7 monthly boluses IV cyclophosphamide plus corticosteroids
- Randomly assigned to maintenance therapy
  » Quarterly IV cyclophosphamide, or
  » Oral azathioprine (1-3 mg/kg BW/day), or
  » Oral MMF (500-3000 mg/day) for 1-3 years

Cumulative Probability of Relapse-Free Survival

- Two Trials of Mycophenolate Mofetil in Lupus Nephritis:
  - U.S. FDA trial
  - ALMS study

Mycophenolate Mofetil U.S. FDA Trial

- Open-label, randomized trial between IV cyclophosphamide and CellCept with a cross-over design
- Enrollment included adults and children from age 13
- 140 patients entered

NIH Study Cytotoxic Therapy Prolongs Renal Survival

- NIH Study
- Cytotoxic Therapy Prolongs Renal Survival

- NIH Study
- Cytotoxic Therapy Prolongs Renal Survival

- NIH Study
- Cytotoxic Therapy Prolongs Renal Survival
Remission rates: MMF vs IVC

Intent-to-Treat analysis

<table>
<thead>
<tr>
<th></th>
<th>MMF</th>
<th>IVC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Remission</td>
<td>16/71</td>
<td>4/69</td>
</tr>
<tr>
<td>Partial Remission</td>
<td>469</td>
<td>21/69</td>
</tr>
<tr>
<td>Complete + Partial Remission</td>
<td>2771</td>
<td>21/69</td>
</tr>
</tbody>
</table>

\[ p = 0.005, p = 0.005, p = 0.009 \]

ALMS: One of the Largest Trials Ever Conducted in Lupus Nephritis

24-wk induction phase

Response or Remission

Yes

MMF 1.5 g BID

IVC 0.5–1 g/m² Monthly

No

No further treatment (exit study)

AZA 2 mg/kg/d

Remission rates: MMF vs IVC

Primary Endpoint:
Renal Response at 6 Months

*Treatment groups were balanced for demographic and baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>MMF (n=185)</th>
<th>IVC (n=185)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients responding (%)</td>
<td>56.2%</td>
<td>53.0%</td>
</tr>
</tbody>
</table>

*AE profile was broadly consistent with that known for each of the drugs

Dosing: Maintenance Phase

- Double-blind, double-dummy design
  - MMF: 1 g BID
  - AZA: 2 mg/kg/d
- Dose adjustment allowed
  - MMF: between 1-3 g/d
  - AZA: between 1-3 mg/kg/d
- Mean Dose
  - MMF: 1.9 g/d
  - AZA: 120 mg/d
- Oral prednisone – maximum of 10 mg/d

Kaplan-Meier Curve
Time to Treatment Failure, N=227

Summary of Treatment Failure Rate by Race

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>White</th>
<th>Black</th>
<th>Asian</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMF Patients with Tx Failure (%)</td>
<td>40</td>
<td>30</td>
<td>40</td>
<td>30</td>
<td>40</td>
</tr>
<tr>
<td>AZA Patients with Tx Failure (%)</td>
<td>30</td>
<td>20</td>
<td>30</td>
<td>20</td>
<td>30</td>
</tr>
</tbody>
</table>
**Summary of Treatment Failure Rate by Induction Treatment**

- MMF superior to AZA in maintaining renal response
- Failure rate at 3 years was 63% for MMF vs 49% for AZA
- Superiority of MMF was consistent regardless of induction treatment, race or region

---

**Randomized Controlled Trial of Prednisone, Cyclophosphamide and Cyclosporine in Lupus Membranous Nephropathy**

- Ghean, Pred, CSA vs. IVCY

---

**Why are biologics needed?**

- No ↓ in proportion of patients with lupus nephritis progressing to ESRD
- Barely 50% of patients with lupus nephritis achieve complete or partial remission with therapy over 6 months
- No ↓ in death rates among lupus cohorts in the last decade

---

**Summary**

- MMF superior to AZA in maintaining renal response
- Failure rate at 3 years was 63% for MMF vs 49% for AZA
- Superiority of MMF was consistent regardless of induction treatment, race or region

---

**Many Patients Do Not Achieve Complete Remission Following Induction**

- Prevalence of Complete Remission in Lupus Nephritis Following Induction Therapy (24 weeks)

- Complete remission defined as return to within 10% of normal values of serum creatinine, proteinuria, and urine sediment.

Source: Ginzler et al. NEJM. 2005
Biologic Therapy for Lupus Nephritis:
The time has come.

Update

Importance of Maintaining Complete Remission in Lupus Nephritis

<table>
<thead>
<tr>
<th>Patient Survival Without ESRD at 10 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Remission</td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>82%</td>
</tr>
</tbody>
</table>

Partial Remission: 50% reduction in baseline proteinuria to < 1.5 g/d with not more than 25% increase in baseline sCr. Complete Remission: Proteinuria < 0.33 g/d and serum creatinine < 1.4 mg/dl


B cell-Targeting Therapies

- Direct B cell-targeting therapies-B-cell depletion
  » rituximab, ocrelizumab (anti-CD20)
  » epratuzumab (anti-CD22)
- B-cell survival molecule BLYS - Indirect B cell-targeting therapies
  » Anti-BLYS: Belimumab
  » Anti-BLYS/April: Atacicept
- Block co-stimulatory interactions between T and B cells
  » Anti-CD40L: BG9588 & IDEC-131 CD40-CD40L, CTLA4Ig

B cell-Targeting Therapies

Systematic review of off-label use of Rituximab in SLE

- 27 uncontrolled studies; n = 456 patients
- Dosing
  » 375 mg/m²/wk x 4 wks (lymphoma schedule)
  » 1000 mg 2 wks apart (RA guidelines)
- 95% of patients achieved good B cell depletion
- Patients may not deplete
  » African Americans
  » High disease activity
  » High human anti-chimeric antibodies (HACA)
  » Low-affinity FcγRIIa
  » Maximal B cell depletion occurs at around 3 months; mean duration 6 months
  » B cell repopulation at around 6-12 months; some lupus patients repopulate at 4 months

Two randomized, double-blind, phase II/III rituximab trials


LUNAR primary end points

- Renal response
  » Complete, partial, or no response at 52 weeks
- Complete renal response
  » Normalization of serum creatinine; if initial creatinine was normal, then ≤ 15% greater than baseline, inactive urinary sediment, and UPC < 0.5
- Partial renal response
  » Serum creatinine ≤ 15% above baseline value, no significant worsening of urinary sediment, and 50% improvement in the UPC

No difference was noted at week 52

![Graph showing comparison between placebo, Rituximab, and Belimumab](image1)

**Belimumab**
- Fully humanized monoclonal antibody
- Selectively targets and inhibits the biological activity of soluble BLyS
- Inhibition of BLyS can result in autoreactive B cell apoptosis

**Update**

![Diagram of Belimumab's effects](image2)

**BILAG Renal Organ System Improvement at Week 52: Pooled Data**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients improved at wk 52, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>50.0</td>
</tr>
<tr>
<td>Belimumab 1 mg/kg</td>
<td>41.7</td>
</tr>
<tr>
<td>Belimumab 10 mg/kg</td>
<td>63.6</td>
</tr>
</tbody>
</table>

In patients with renal A or B score and active renal disease at baseline. Improvement defined as step down from baseline BILAG A or B score to C or D at wk 52; patients on combination or anti-protocol- prohibited medications with consensus to both of approaches.

**Update**

![Graph showing proteinuria reduction](image3)

**Median % ↓ in Proteinuria at Week 52: Pooled Data**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median % reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-20</td>
</tr>
<tr>
<td>Belimumab 1 mg/kg</td>
<td>-48.3</td>
</tr>
<tr>
<td>Belimumab 10 mg/kg</td>
<td>-60</td>
</tr>
</tbody>
</table>

p = 0.054 for belimumab 1 mg/kg vs placebo in patients with baseline proteinuria ≥0.5 g/24 h.

**Treatment algorithm for resistant lupus nephritis**

Resistance indicates 25% decrease in eGFR or ESRD, 100% in urine protein-creatinine ratio, or presence of active urinary sediment.

**Update**

- 298 patients: placebo OR abatacept (10 mg/kg) OR abatacept at 30 mg/kg x 3 mos, followed by standard weight-tiered dose (30/10)
- Primary endpoint: time to confirmed complete response and inactive urine sediment
- No differences between treatment arms in time to confirmed complete response
- ~20-30% greater reduction in UP/C not associated with risk of infections
MPGN and C3 Glomerulopathy

Dense deposit disease is associated with increased activity of:

A. C1
B. C4
C. C3
D. C6
E. C5b-9

Type I MPGN
- Idiopathic
- Secondary to:
  - Chronic/indolent bacterial infection
  - SBE, osteomyelitis, mastoiditis
  - Infected indwelling catheters and shunts
  - Hepatitis C and less frequently hepatitis B
  - Cryoglobulinemia (types I and II)
  - Malignancies
    - Carcinoma, sarcoma, lymphoma, leukemia
    - Monoclonal IgG MPGN
  - C2 or C3 deficiency
  - C3 glomerulopathy (C regulatory defect; e.g., deficient CFH)

Membranoproliferative Glomerulonephritis Type I

Light Microscopy

Immunofluorescence Microscopy

Membranoproliferative Glomerulonephritis (I)
- subendothelial immune complex dense deposits
- subendothelial mesangial interposition

Type II Membranoproliferative GN

Dense Deposit Disease (DDD)

Type II Membranoproliferative GN
Dense Deposit Disease (DDD)
Type II Membranoproliferative GN
• Idiopathic
• Secondary to:
  » Complement regulatory protein deficiency caused by genetic mutations
  » Autoantibodies against complement regulatory proteins (e.g. anti-CFH)
  » C3 nephritic factor autoantibodies (C3NeF)
  » Familial and acquired partial lipodystrophy (usually with C3NeF)

Note: Some DDD does not have a MPGN pattern.

Schematic depiction of the complement pathways
The complement system can be activated via the classical or alternative pathways which converge to form C3 convertase, the central point of the complement cascade. The alternative pathway is continually active at low levels in circulation (basal) by spontaneous hydrolysis of the thioester bond of C3 (so-called "tick over" mechanism), resulting in generation of C3b.

Acquired and Genetic Abnormalities Associated with Complement-Mediated MPGN
Acquired abnormalities include antibodies to complement-regulating proteins, such as antibodies to C3 convertase (C3c) (C3NeF). Genetic abnormalities include mutations in genes involved in complement-regulating proteins, including CFHR, CFH, MCP, and C3 NeF.

MPGN by LM
- Immunoglobulin and C3 deposits by IF
- C3 deposits but no immunoglobulin deposits by IF
- Infection
- Autoimmunity
- Alternative pathway dysregulation with complement or complement-regulating protein mutations or antibodies

Eculizumab in Dense-Deposit Disease
  » E. Daina, M. Noris, G. Remuzzi; Bergamo, Italy
  » M. Vivarelli, F. Emma, Rome Italy; A. Pasini, Bologna Italy

Update
Eculizumab in C3 Glomerulonephritis and Dense Deposit Disease

- ↓ glomerular endocapillary proliferation and neutrophil infiltration
- No significant diminution in staining for C3 or C5b-9
- No resolution of glomerular dense deposits after 1 yr of therapy
- Eculizumab appears to bind to and deposit within glomeruli, basement membrane and vessel walls of treated patients


ANCA-SMALL VESSEL VASCULITIS

ANCA Vasculitis

- What is the most predictive marker of relapse in ANCA vasculitis?
  A. MPO-ANCA and rapidly progressive glomerulonephritis
  B. MPO-ANCA and upper respiratory tract disease
  C. PR3-ANCA and lung disease
  D. PR3-ANCA and skin disease

Query

2012 Chapel Hill Consensus Conference Vasculitis Nomenclature

Revised Chapel Hill Nomenclature

- Large vessel vasculitis (LVV)
  - Takayasu arteritis (TA)
  - Giant cell arteritis (GCA)
- Medium vessel vasculitis (MVV)
  - Polyarteritis nodosa (PAN)
  - Kawasaki disease (KD)
- Small vessel vasculitis (SVV)
  - Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV)
  - Microscopic polyangiitis (MPA)
  - Granulomatosis with polyangiitis (Wegener's) (GPA)
  - Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA)
  - Immune complex SVV
  - Anti-glomerular basement membrane (anti-GBM) disease
  - Cryoglobulinemic vasculitis (CV)
  - IgA vasculitis (Henoch-Schönlein) (IgAV)
  - Hypocomplementemic urticarial vasculitis (anti-C1q vasculitis)
  - Variable vessel vasculitis (VVV)
  - Behcet's disease (BD)
  - Cogan's syndrome (CS)
- Single-organ vasculitis (SOV)
  - Cutaneous leukocytoclastic angiitis
  - Cutaneous arteritis
  - Primary central nervous system vasculitis
  - Isolated aortitis
  - Others
- Vasculitis associated with systemic disease
  - Arthritis
  - Diabetes mellitus
- Vasculitis associated with probable etiology
  - Hepatitis C virus-associated cryoglobulinemic vasculitis
  - Hepatitis B virus-associated vasculitis
  - Syphilis-associated aortitis
  - Drug-associated immune complex vasculitis
  - Drug-associated ANCA-associated vasculitis
  - Cancer-associated vasculitis
  - Others

Patients with PR3-ANCA are genetically different from patients with MPO-ANCA.

Clinical Syndromes Analyzed by ANCA Specificity


<table>
<thead>
<tr>
<th>Population Cohorts</th>
<th>DRB1*15 Positive</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>African American PR3-ANCA</td>
<td>22/25 (88%)</td>
<td>35.9</td>
<td>3.0 x 10^-11</td>
<td></td>
</tr>
<tr>
<td>African American MPO-ANCA</td>
<td>3/25 (12%)</td>
<td>0.7</td>
<td>0.76</td>
<td></td>
</tr>
<tr>
<td>Caucasian PR3-ANCA</td>
<td>23/74 (31%)</td>
<td>2.2</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>Caucasian MPO-ANCA</td>
<td>4/22 (18%)</td>
<td>1.1</td>
<td>0.77</td>
<td></td>
</tr>
</tbody>
</table>


Patients with PR3-ANCA are phenotypically different from patients with MPO-ANCA.

Frequency of C/PR3 and P/MPO ANCA by clinical phenotype

PR3-ANCA patients relapse much more frequently than MPO-ANCA patients.

### Multivariate Models of Predictors of Relapse

<table>
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<th>Consistent Predictors of Relapse</th>
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</tr>
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</tr>
<tr>
<td>With any of the above</td>
<td>1.8 (1.0, 3.5)</td>
</tr>
</tbody>
</table>


### Cutaneous Manifestations of Vasculitis

- Purpura
- Petechiae
- Ecchymoses
- Erythematous macules
- Papules
- Nodules
- Urticaria
- Livedo reticularis
- Necrosis
- Ulceration
- Vesicles
- Bullae
- Pyoderma gangrenosum-like lesions
- Erythema nodosum-like lesions
- Sweet’s like lesions

### Upper Respiratory Tract Symptoms in ANCA-GN Patients

- Sinusitis
- Otitis media
- Cranial nerve entrapment
- Subglottic stenosis
- Nasal ulcers and crusting

### Renal-Dermal Syndrome

- Systemic lupus erythematosus
- Henoch-Schönlein purpura
- ANCA-positive vasculitis
- Cryoglobulinemia
10% of ANCA patients clot

- Subset of PR3-ANCA patients have anti-plasminogen antibodies
- PR3-ANCA patient developed DVT; has anti-cPR3 antibodies that inhibit plasmin activity
- PR3-ANCA patient did not develop DVT; has anti-cPR3 antibodies that DO NOT inhibit plasmin activity
- PR3 and plasminogen are complementary proteins

Signs and Symptoms of Necrotizing Small Vessel Vasculitis

- Cutaneous purpura, nodules and ulcerations
- Peripheral neuropathy (mononeuritis multiplex)
- Abdominal pain and blood in stool
- Hematuria, proteinuria and renal insufficiency
- Hemoptysis and pulmonary infiltrates or nodules
- Necrotizing (hemorrhagic) sinusitis
- Myalgias and arthralgias
- Muscle and pancreatic enzymes in blood

Contaminated Cocaine and Drug-Induced Vasculitis

- Cutaneous vasculitis syndrome attributed to cocaine contaminated with the adulterant levamisole
- Usually positive for both MPO and PR3
  » 11/11 dual positive patients identified at Mass General were positive for cocaine exposure
- Typically characterized by a retiform purpuric skin rash accompanied by leukopenia and autoantibody production

WHAT IS THE MOST EFFECTIVE, LEAST TOXIC INDUCTION THERAPY?

Conventional Treatment of ANCA Vasculitis

- IV pulse methylprednisolone 7 mg/kg x 3 days
- Prednisone 1 mg/kg X 4 weeks then tapered with either
- IV cyclophosphamide 0.5 g/m² X 6 months
  or
- Oral cyclophosphamide 2 mg/kg* X 6 to 12 months

  *adjusted based on leukocyte count

Risk Factors for Death and ESRD in Patients with ANCA-NCGN and MPA

<table>
<thead>
<tr>
<th>Feature</th>
<th>Risk of Death</th>
<th>Risk of ESRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoptysis</td>
<td>8.6 (p = 0.0002)</td>
<td></td>
</tr>
<tr>
<td>Lung disease</td>
<td>2.4 (p = 0.61)</td>
<td>1.0 (p = 0.97)</td>
</tr>
<tr>
<td>MPA vs. GN</td>
<td>1.7 (p = 0.61)</td>
<td>1.0 (p = 0.93)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>2.6 (p = 0.0002)</td>
<td></td>
</tr>
<tr>
<td>GN activity</td>
<td>1.1 (p = 0.16)</td>
<td></td>
</tr>
<tr>
<td>GN chronicity</td>
<td>1.1 (p = 0.24)</td>
<td></td>
</tr>
</tbody>
</table>

Efforts to Remove Autoantibody

- Plasmapheresis
- Anti-B cell therapy
- Pooled IV Ig

- In general, remission rates are on the order of 70-93%
- Relapse rates vary from 0% to 50%

MEPEX Trial

- Plasma exchange (PE) versus pulsed methylprednisolone as adjunctive therapy (ivMeP) with initial creatinine > 500 µmol
- 151 patients given either:
  - 7 PE treatments of 60 ml/kg each within the first two weeks, or
  - 3 pulses of ivMeP 15 mg/kg each
  - in addition to oral cyclophosphamide and tapering prednisolone regimen

MEPEX Trial Outcomes

- Renal outcome at 3 months significantly better in PE-treated group, most marked in patients dialysis-dependent at presentation
- Renal outcome at 5 years better

PEXIVAS Trial

- Multicenter, open label, factorial design, RCT, n=500
- To determine:
  - Efficacy of PLEX + immunosuppressive therapy + glucocorticoids (GC) in reducing death
  - Non-inferiority of reduced dose GC in reducing death and ESRD
- Patients must have active pulmonary hemorrhage and/or renal disease
- Randomized to receive either:
  - Adjunctive PLEX or no PLEX, and
  - Standard or low GC dose
- Induction therapy with cyclophosphamide or rituximab + corticosteroids
- Primary outcomes: all-cause mortality and ESRD

Plasmapheresis could be used for severe pulmonary bleeding and near-dialysis-dependent renal disease

Little evidence that plasmapheresis is superior to methylprednisolone for everyone else
WHAT IS THE MOST EFFECTIVE, LEAST TOXIC THERAPY TO ACHIEVE A REMISSION?

Corticosteroids Alone Do Not Work

- Remission rate
  - cyclophosphamide 85%
  - corticosteroids 56% (p = 0.003)
- Risk of relapse increased 3-fold in corticosteroids alone group
  - (RP = 3.2, 95% CI, 1.2, 8.3*)
  - *controlling for age, serum creatinine, duration of treatment, and presence of arteriosclerosis on biopsy

CYCLOPS - Study Design

**Induction**
- AZA + Prednisone
- CP 2mg/kg/d po —> 1.5 mg/d

**Consolidation**
- IV CP 15 mg/kg/pulse
- Oral Prednisolone (mg/d) 60 25 12.5 7.5

**Maintenance**
- CP 2mg/kg/d po —> 1.5 mg/d


CYCLOPS: Results

<table>
<thead>
<tr>
<th></th>
<th>IVCP</th>
<th>Oral CP</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-free interval</td>
<td>15.0 m</td>
<td>13.5 m</td>
<td>(ns)</td>
</tr>
<tr>
<td>Time to remission</td>
<td>3 m</td>
<td>3 m</td>
<td>(ns)</td>
</tr>
<tr>
<td>Time to relapse</td>
<td>8.5 m</td>
<td>7.3 m</td>
<td>(ns)</td>
</tr>
<tr>
<td>Survival</td>
<td>93%</td>
<td>86%</td>
<td>(ns)</td>
</tr>
<tr>
<td>Cumulative CP dose</td>
<td>1</td>
<td>2</td>
<td>(&lt;.05)</td>
</tr>
</tbody>
</table>


CYCLOPS: Revisited

Pulse cyclophosphamide is associated with a higher relapse risk than DO cyclophosphamide. However, this is not associated with increased mortality or long-term morbidity. Although the study was retrospective, data was returned in 90% of patients from the original trial.


Update

Pulse cyclophosphamide is associated with a higher relapse risk than DO cyclophosphamide. However, this is not associated with increased mortality or long-term morbidity. Although the study was retrospective, data was returned in 90% of patients from the original trial.

Strategies for Avoiding Oral Cytoxan

• Use less of it by giving it IV
• Use it for a shorter duration of time
• Prevent relapses
• Substitute other drugs

Controlled Trials of Maintenance Therapy in Generalized Vasculitis

• IMPROVE: Azathioprine > mycophenolate mofetil 2 g p.o. until month 42 (Hiemstra TF et al. JAMA 2010; 304(21):2381-2388)
• REMAIN: Azathioprine until month 42 then stop

Rituximab vs. Cyclophosphamide in ANCA Vasculitis

• RITUXIVAS
  » Rituximab + IV cyclophosphamide vs. IV cyclophosphamide
• RAVE
  » Rituximab + glucocorticoids vs. oral cyclophosphamide

RAVE

• 6 months of rituximab and glucocorticoids compared with 6 months of oral cyclophosphamide
• 64% of the patients assigned to rituximab achieved primary outcome compared with 53% in the cyclophosphamide arm
• Rituximab was more efficacious than cyclophosphamide among patients with relapsing disease 66.7% vs. 42.0%
• Adverse events were similar between the rituximab and cyclophosphamide groups

Hard to “RAVE” about treatment of ANCA vasculitis

Efficacy of Remission-Induction Regimens for ANCA-Associated Vasculitis

<table>
<thead>
<tr>
<th>Time (mos)</th>
<th>Rituximab (N=16)</th>
<th>Cyclophosphamide (N=16)</th>
<th>Difference</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 mos</td>
<td>45 (94)</td>
<td>52 (31)</td>
<td>7 (3-34)</td>
<td>0.13</td>
</tr>
<tr>
<td>1 mos</td>
<td>47 (47)</td>
<td>18 (11)</td>
<td>29 (5-30)</td>
<td>0.02</td>
</tr>
<tr>
<td>2 mos</td>
<td>19 (56)</td>
<td>12 (13)</td>
<td>7 (7-20)</td>
<td>0.12</td>
</tr>
</tbody>
</table>
The jury is still out...

- 24 clinical trials reviewed using rituximab for induction of remission or maintenance of remission
- Conclusions:
  » Small to moderate patient enrollment (6 to 99 patients)
  » Improved biomarkers would aid in selection of dose and dosing interval
  » Beneficial effects of rituximab over standard therapy have not been shown on vasculitis-related damage (loss of GFR, mortality, or quality of life)

- It is not clear that rituximab is safer in the short-term or long-term than oral cyclophosphamide
- It is not clear that rituximab works as quickly as cyclophosphamide to preserve glomeruli

ANCA (+)
- Hematuria
- Skin rash
- Vasculitis
- Pulmonary infiltrates
- Creatinine 1.2 mg/dL

September 2012

- Gram (-) sepsis
- No hematuria

January 2013

- Oral cyclophosphamide

60 mg prednisone + IV cyclophosphamide

November 2012

- Creatinine 2.5 mg/dL
- Biopsy: necrotizing vasculitis

December 2012

Rituximab x 4 doses

Strategies for Avoiding Oral Cytoxan

- Use less of it by giving it IV
- Use it for a shorter duration of time
- Prevent relapses
- Substitute other drugs

WORRYING ABOUT OVER-IMMUNOSUPPRESSION

WORRYING ABOUT OVER-IMMUNOSUPPRESSION

CYCAZAREM Trial Complications

- Severe adverse events:
  » 8 deaths during induction
  » and in 15 additional patients during remission phase, there were severe adverse effects
    » 8 patients in azathioprine group
    » 7 patients in cyclophosphamide group
**Wegener’s Granulomatosis**

**Etanercept Trial (WGET)**

- No significant differences between etanercept and control groups in:
  - sustained remission rates (69.7 vs. 76.3%, p=0.39)
  - sustained periods of low-level disease activity (86.5 vs. 90.6%, p=0.32)
  - time to achieve those measures
- Disease flares were common in both groups
- 56.2% of patients in the etanercept group and 57.1% in the control group had at least one severe adverse event or died
- Solid cancers developed in 6 patients in the etanercept group, but none in the control group (p=0.01)

**Current Therapy**

- Plasmapheresis
  - or
- IV methylprednisolone
  - then
- IV cyclophosphamide and/or
  - Rituximab
  - then
  - Azathioprine
  - and/or
  - Stop

- Use antibiotic therapy to decrease upper respiratory tract disease
- Use the smallest dose of immunosuppressive therapy, and in only those who need it
- Carefully monitor signs of relapse in all patients

**Multivariate Models of Predictors of Relapse**

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### Multivariate Predictors of Relapse in the GDCN and French ANCA Vasculitis Cohorts

<table>
<thead>
<tr>
<th></th>
<th>GDCN cohort (n=350)</th>
<th>French cohort (n=434)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>PR3 vs. MPO ANCA antibody status</td>
<td>1.77 (1.11-2.82)</td>
<td>0.017</td>
</tr>
<tr>
<td>Lung involvement</td>
<td>1.68 (1.10-2.57)</td>
<td>0.017</td>
</tr>
<tr>
<td>Upper respiratory tract involvement</td>
<td>1.58 (1.00-2.66)</td>
<td>0.046</td>
</tr>
<tr>
<td>Lung involvement and PR3 vs. MPO ANCA antibody status</td>
<td>2.46 (1.60-3.77)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>


### Treatment Options for AAV

- Induction Therapy
- Maintenance Immunosuppression
- Remission Therapy
- Remission Maintenance
- Follow-up