Primary & Secondary Glomerular Disease

John Feehally
GLOMERULONEPHRITIS

Immune disease which mainly affects glomeruli

Renal biopsy required to make the diagnosis
ISSUES IN GLOMERULONEPHRITIS

Terminology

Classification

Aetiology

Natural History

Treatment
ISSUES IN GLOMERULONEPHRITIS

Terminology

Classification

Aetiology

Natural history

Treatment
TERMINOLOGY IN GLOMERULONEPHRITIS

Glomerulonephritis

or

Glomerular disease
TERMINOLOGY IN GLOMERULONEPHRITIS

Primary ?

Secondary ?
TERMINOLOGY IN GLOMERULONEPHRITIS

Different names for the same thing…..

Minimal change nephrotic syndrome

Minimal change disease

Lipoid nephrosis

Idiopathic nephrotic syndrome

Minimal change glomerulonephritis
ISSUES IN GLOMERULONEPHRITIS

Terminology

Classification

Aetiology

Natural History

Treatment
CLASSIFICATION OF GLOMERULONEPHRITIS

- Histopathology
- Clinical
- Immune mechanisms
CLASSIFICATION OF GLOMERULONEPHRITIS

Histopathology

Clinical

Immune mechanisms

Patterns established on light microscopy

- Membranous
- Mesangiocapillary
- Focal segmental glomerulosclerosis
- etc……
CLASSIFICATION OF GLOMERULONEPHRITIS

Histopathology

Clinical

Immune mechanisms

Patterns established on light microscopy
- Membranous
- Mesangiocapillary
- Focal segmental glomerulosclerosis
  
‘Patterns’ not ‘diseases’
PATHOLOGICAL CLASSIFICATION OF GLOMERULONEPHRITIS

- Light microscopic appearance
  e.g. MEMBRANOUS NEPHROPATHY

- Type of immune deposits
  e.g. IgA NEPHROPATHY
ISSUES IN GLOMERULONEPHRITIS

Terminology
Classification
Aetiology
Natural History
Treatment
AETIOLOGY OF GN

INFECTION

- the dominant aetiological agent for GN in the developing world
POST-STREPTOCOCCAL GLOMERULONEPHRITIS

Epidemic Streptococcal infection

Nephritogenic Streptococci

Impaired host response

PSGN
MEMBRANOUS NEPHROPATHY

DEVELOPING WORLD
- HBV
- Leprosy
- Syphilis
- Hydatid disease
- Malaria
- Schistosomiasis

DEVELOPED WORLD
- Idiopathic
- Drugs
- Malignancy
- Lupus
- Infections
CHRONIC INFECTION AND GN

Commonest histological pattern
Mesangiocapillary [membranoproliferative] GN type 1

Pattern of GN associated with a wide range of chronic infections

- Infective endocarditis
- ‘Shunt’ nephritis
- Schistosomiasis

...
CHANGING PREVALENCE OF MCGN

CHRONIC INFECTION AND GN

Commonest histological pattern
Mesangiocapillary [membranoproliferative] GN type 1

DEVELOPED WORLD

Incidence falling

Emergence of HCV as a causative agent
AETIOLOGY OF GN

INFECTION

Dominant aetiological agent for GN in the developing world

VARIED HOST RESPONSE

Same infection → different patterns of GN

Same pattern of GN ← different infection
AETIOLOGY OF GN

The developed world

Are the common patterns of GN caused by infections we have not yet identified?

Are other environmental antigens involved?

Do changing patterns of GN reflect changing patterns of host immunity in urbanised culture?
AETIOLOGY OF GN

Infection

Other identifiable environmental antigens
AETIOLOGY OF GN

Infection

Other identifiable environmental antigens

Auto-immunity
GOODPASTURE’S DISEASE – ANTI-GBM DISEASE

The circulating anti-GBM IgG antibody is directly pathogenic

Transfer experiments

Depletion of antibody is therapeutic
LUPUS NEPHRITIS

The archetypal ‘immune complex’ disease

.... although the antigens involved in the complexes remain incompletely defined

Highly variable expression of renal disease
AETIOLOGY OF GN

- Infection
- Other identifiable environmental antigens
- Auto-immunity
- Other
ALTERED IgA1 O-GLYCOSYLATION IN IgA NEPHROPATHY

Hinge region

A plausible site for a pathogenic abnormality

Hinge has unusual O-glycosylation

Hinge O-glycosylation abnormal in:
Serum IgA1 & mesangial IgA1 in IgAN
AETIOLOGY OF GN

Infection

Other identifiable environmental antigens

Auto-immunity

Other

Genetics
DISEASE MECHANISMS IN GLOMERULONEPHRITIS

Genetics → Infection → Auto-immunity → Immune injury → Inflammation → Resolution → Unknown
PATHOGENESIS OF GN

Evidence from renal transplantation

Some patterns of GN have always recurred despite innovative anti-rejection therapy
ISSUES IN GLOMERULONEPHRITIS

Terminology
Classification
Aetiology
Natural History
Treatment
INTPRETING NATURAL HISTORY STUDIES & TREATMENT TRIALS IN GLOMERULONEPHRITIS

Patterns or diseases?
Changing incidences?
Worldwide variations?
Inclusion criteria?
Disease onset?
Therapeutic effects?
INTERPRETING NATURAL HISTORY STUDIES IN GLOMERULONEPHRITIS

Patterns or diseases ?
Changing incidences ?
Worldwide variations ?
Inclusion criteria ?
Disease onset ?
Therapeutic effects ?

Benefit of female gender

...mostly explained by lower proteinuria & BP throughout follow up

Catran D et al. NDT 2008; 23: 2247
ISSUES IN GLOMERULONEPHRITIS

Terminology
Classification
Aetiology
Natural History
Treatment
WHY IS POST-STREPTOCOCCAL GN NOW SO UNCOMMON IN THE DEVELOPED WORLD?
WHY IS POST-STREPTOCOCCAL GN NOW SO UNCOMMON IN THE DEVELOPED WORLD?

The progress of immunology?
WHY IS POST-STREPTOCOCCAL GN NOW SO UNCOMMON IN THE DEVELOPED WORLD?

The progress of immunology?
WHY IS POST-STREPTOCOCCAL GN NOW SO UNCOMMON IN THE DEVELOPED WORLD?

The progress of immunology? X

Antibiotics?
WHY IS POST-STREPTOCOCCAL GN NOW SO UNCOMMON IN THE DEVELOPED WORLD?

The progress of immunology?  X

Antibiotics?  X
WHY IS POST-STREPTOCOCCAL GN NOW SO UNCOMMON IN THE DEVELOPED WORLD?

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Antibiotics? X

Public health?
WHY IS POST-STREPTOCOCCAL GN NOW SO UNCOMMON IN THE DEVELOPED WORLD?

The progress of immunology? X

Antibiotics? X

Public health? YES
WHY IS POST-STREPTOCOCCAL GN NOW SO UNCOMMON IN THE DEVELOPED WORLD?

The progress of immunology?  X

Antibiotics?  X

Public health?  YES

Spontaneous changes in streptococcal types?  ?
PREVENTION OF INFECTION-RELATED GN

Progress with infection control

Schistosomiasis

Malaria

HBV
Progress with infection control

Schistosomiasis

Malaria

HBV

DURBAN, SOUTH AFRICA

HBV childhood immunisation from 1995 – incomplete coverage

Incidence of HBV-associated MN reduced by 80%
After 1998: no child age < 4 years

Bhimma R et al. 2003
Why are we still treating these diseases with immunosuppressive drugs introduced into clinical practice..

..while I was still at school?
Why are we still treating these diseases with immunosuppressive drugs introduced into clinical practice..

..while I was still at school ?

... and which can be toxic ?
Why are we still treating these diseases with immunosuppressive drugs introduced into clinical practice...

..while I was still at school?

... and which can be toxic?

CORTICOSTEROIDS

CYCLOPHOSPHAMIDE

AZATHIOPRINE
IMMUNE TREATMENT FOR GLOMERULONEPHRITIS

SIDE EFFECTS OF TREATMENT
- Cushingism
- Opportunistic infection
- Infertility
- Osteopenia
- Secondary neoplasia

IMPLICATIONS OF RENAL FAILURE
- Cardiovascular morbidity
- Infertility
- Transplant recurrence
- Quality of life
Lack of

PROGRESS IN TREATMENT OF GN

Transience of initiating events

Failure to learn lessons from recurrence after transplantation

Broad effects of existing immune therapy
Lack of progress in treatment of GN

Newer immunosuppressives have been developed for transplantation

Focus on suppressing T cell driven alloimmunity
Lack of progress in treatment of GN

Complexity and redundancy of inflammatory and anti-inflammatory pathways
NEW TREATMENTS OF GLOMERULONEPHRITIS

POTENTIAL TARGETS

- T cells
- Macrophages
- Cytokines
- Adhesion molecules
- Chemokines
- Profibrotic growth factors
NEW TREATMENTS OF GLOMERULONEPHRITIS

POTENTIAL TARGETS

- T cells
- Macrophages
- Cytokines
- Adhesion molecules
- Chemokines
- Profibrotic growth factors

PROBLEMS

- Development costs
- Timing
- Kidney-specific delivery
- Need multiple interventions
Lack of PROGRESS IN TREATMENT OF GN

Why have there been so few RCT’s in this field?
Lack of

PROGRESS IN TREATMENT OF GN

Why have there been so few RCT’s in this field?

Uncommon
Lack of

PROGRESS IN TREATMENT OF GN

Why have there been so few RCT’s in this field?

Uncommon

Slowly progressive
Lack of PROGRESS IN TREATMENT OF GN

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Opinion
Lack of

PROGRESS IN TREATMENT OF GN

Why have there been so few RCT’s in this field?

Uncommon

Slowly progressive

Opinion

‘Precious patients’
Active treatment does not only mean immunosuppression. Symptoms can be relieved and renal failure may be delayed.
TREATMENT OF GLOMERULONEPHRITIS

No steroids or immunosuppressives does not = no treatment

- Blood pressure
- Oedema
- Proteinuria
- Cholesterol
- Smoking
GLOMERULAR DISEASE
GLOMERULAR DISEASE

- Minimal change/FSGS
- Membranous
- MCGN
- IgA nephropathy
- Post-infectious GN
GLOMERULAR DISEASE

Minimal change/FSGS
Membranous
MCGN
IgA nephropathy
Post-infectious GN

Lupus
Vasculitis
Henoch-Schönlein nephritis
Cryoglobulinaemia
Anti-GBM nephritis
GLOMERULAR DISEASE

Minimal change/FSGS
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Thrombotic microangiopathy
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Amyloid, MIDD & fibrillary GN
GLOMERULAR DISEASE

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Diabetic nephropathy

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Amyloid, MIDD & fibrillary GN

Diabetic nephropathy

HEREDITARY
Alport
Fabry
Nail-patella
LCAT deficiency
etc..

etc.
GLOMERULAR DISEASE

- Minimal change/FSGS
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  - MCGN
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GLOMERULAR DISEASE

Minimal change/FSGS
Membranous
MCGN
IgA nephropathy
Post-infectious GN

Lupus
Vasculitis
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Diabetic nephropathy

HEREDITARY
Alport
Fabry
Nail-patella
LCAT deficiency
etc..

Thrombotic microangiopathy
Amyloid, MIDD & fibrillary GN
MINIMAL CHANGE DISEASE IN ADULTS

• 10-20% of adults with nephrotic syndrome (cf children 90%)

• Spontaneous remission occurs in 5-10% of cases within 2 months

• Non-nephrotic proteinuria does not respond well to immunosuppression
MINIMAL CHANGE DISEASE IN ADULTS

- 10-20% of adults with nephrotic syndrome (cf children 90%)

- Spontaneous remission occurs in 5-10% of cases within 2 months

- Non-nephrotic proteinuria does not respond well to immunosuppression

Is this the same disease?
TREATMENT OF MINIMAL CHANGE DISEASE IN ADULTS

SPECIFIC THERAPY

• Few controlled trial in adults

• Guidelines extrapolated from studies in children and cohort studies

• Controversies in corticosteroid therapy
  – Time to response
  – Dosage & duration of corticosteroids
CORTICOSTEROIDS for MINIMAL CHANGE DISEASE
TIME TO REMISSION IN ADULTS AND CHILDREN

WHY SUCH VARIANCE?
Steroid dosing?
Identifying FSGS?
MINIMALCHANGE DISEASE IN ADULTS
Course after steroid treatment

- ~50% will have at least one relapse
- 10-25% frequently relapse
- 25-30% are steroid dependent
MINIMALCHANGE DISEASE IN ADULTS
Second line therapy for frequent relapsing/steroid dependence

**Corticosteroids**
- Low dose alternate day regimens

**Cyclophosphamide**
- 12 weeks - 2mg/kg/day (cumulative ‘safe’ dose of 150-250mg/kg)
- Ideally commence following induction of remission

**Cyclosporin**
- 3-5mg/kg/day (trough level 50-150ng/ml)
- May be first choice in younger patients
- Response within 3 months
- If effective try to withdraw after 1 year
FSGS first described by Habib and others

...correlating histology findings with response to corticosteroids
### Causes of Adult Nephrotic Syndrome

<table>
<thead>
<tr>
<th></th>
<th>1976-9</th>
<th>1995-7</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>White</td>
<td>Black</td>
</tr>
<tr>
<td>Membranous</td>
<td>38%</td>
<td>34%</td>
</tr>
<tr>
<td>Minimal change</td>
<td>22%</td>
<td>19%</td>
</tr>
<tr>
<td>FSGS</td>
<td>9%</td>
<td>30%</td>
</tr>
<tr>
<td>IgAN</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>MCGN</td>
<td>8%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Haas AJKD 1997; 30: 621
FSGS IN WEST AFRICA

SENEGAL
115 biopsies 1993-98

Two thirds - nephrotic syndrome

Primary GN

47% FSGS

12.5% Membranous

FOCAL SEGMENTAL GLOMERULOSCLEROSIS

An histological pattern …… *not* a diagnosis
PATHOLOGICAL CLASSIFICATION OF FSGS

Classic FSGS

Perihilar variant

Cellular variant

Collapsing variant

Tip variant
Does steroid responsiveness define a ‘disease’?

Is it more important than presence of FSGS?

Can minimal change ‘evolve’ into FSGS?
CLINICAL PRESENTATIONS OF FSGS

PRIMARY FSGS

Typically ‘like minimal change’:

Sudden onset of nephrotic syndrome

Any age –
but commonest in children
and young adults
CLINICAL PRESENTATIONS OF FSGS

PRIMARY FSGS
Typically ‘like minimal change’:
Sudden onset of nephrotic syndrome
Any age – but commonest in children and young adults

SECONDARY FSGS
More often:
Asymptomatic proteinuria
Normal serum albumin
Any age
Secondary FSGS
Drugs

- Intravenous heroin
- Pamidronate
- Interferon-α

Secondary FSGS
Viruses
- HIV
- Parvovirus B19

Drugs
- Intravenous heroin
- Pamidronate
- Interferon-α

Secondary FSGS
**Viruses**
- HIV
- Parvovirus B19

**Drugs**
- Intravenous heroin
- Pamidronate
- Interferon-α

**Secondary FSGS**

**Adaptive response to reduced renal mass**
- Renal agenesis/dysplasia
- Oligomeganephronia
- Surgical renal ablation
- Reflux nephropathy
- Cortical necrosis
- Chronic allograft nephropathy
- Any advanced renal disease with reduction in functioning nephrons
Adaptive response with initially normal renal mass

- Obesity
- Sickle cell nephropathy
- Congenital cyanotic heart disease

Adaptive response to reduced renal mass

- Renal agenesis/dysplasia
- Oligomeganephronia
- Surgical renal ablation
- Reflux nephropathy
- Cortical necrosis
- Chronic allograft nephropathy
- Any advanced renal disease with reduction in functioning nephrons

Secondary FSGS

Viruses

- HIV
- Parvovirus B19

Drugs

- Intravenous heroin
- Pamidronate
- Interferon-α
Primary (Idiopathic) FSGS

Genetic FSGS

Secondary FSGS
Primary FSGS  (Idiopathic)

Genetic FSGS

Secondary FSGS
Autosomal recessive FSGS
Sporadic steroid-resistant FSGS
  Children > adults

Autosomal dominant FSGS

Sub-nephrotic proteinuria

Autosomal dominant FSGS

? sporadic FSGS
PREDICTIONS

FSGS associated with podocyte protein mutations
PREDICTIONS

FSGS associated with podocyte protein mutations

... will be steroid resistant
PREDICTIONS

FSGS associated with podocyte protein mutations

... will be steroid resistant

... will not recur in transplants
PATHOGENESIS OF FSGS

Lessons from transplant recurrence
PATHOGENESIS OF FSGS

Lessons from transplant recurrence

RECURRENCE is not inevitable
Lessons from transplant recurrence

RECURRENCE is not inevitable

CLINICAL recurrent proteinuria may be immediate
……implies ‘circulating factor’
PATHOGENESIS OF FSGS

Lessons from transplant recurrence

RECURRENCE
is not inevitable

CLINICAL
recurrent proteinuria may be immediate
......implies ‘circulating factor’

PATHOLOGICAL
After one month of recurrence
there may be foot process effacement
......but no segmental lesions
PATHOGENESIS OF PRIMARY FSGS

Genetics

Circulating factor[s]

Second [or third] ‘hit’
PRIMARY FSGS

Can we predict outcome at presentation?

Does spontaneous remission occur?

Can we select which patients should receive corticosteroids?
PRIMARY FSGS

Can we predict outcome at presentation?

Histology

Genetics

Clinical
PRIMARY FSGS

Can we predict outcome at presentation?

HISTOLOGY

Tip lesion

Collapsing variant

Number of glomeruli with segmental / global sclerosis?

Tubular atrophy & interstitial fibrosis
FSGS – HISTOLOGICAL VARIANTS & OUTCOME

Thomas DB et al. KI 2006; 69: 920
PRIMARY FSGS

Can we predict outcome at presentation?

GENETICS

Not yet ......
PRIMARY FSGS

Can we predict outcome at presentation?

IMPORTANCE OF PROTEINURIA

<table>
<thead>
<tr>
<th>Non-nephrotic</th>
<th>20% ESRD at 10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrotic</td>
<td>&gt;50% ESRD at 5-10 years</td>
</tr>
<tr>
<td>Nephrotic &gt;10g/day</td>
<td>~100% ESRD at 5-10 years</td>
</tr>
</tbody>
</table>

Malignant FSGS
PRIMARY FSGS

Survival according to remission

5yr survival
94% v 52%

PROGNOSIS IN NEPHROTIC PRIMARY FSGS

Rydel et al. AJKD 1995; 25: 534
TREATMENT OF
NEPHROTIC PRIMARY FSGS
TREATMENT OF PRIMARY FSGS

- Renin-angiotensin blockade
- BP control
- Statins
TREATMENT OF PRIMARY FSGS

Renin-angiotensin blockade
BP control
Statins

IMMUNOSUPPRESSION

Corticosteroids
Cyclophosphamide
Cyclosporine
TREATMENT OF PRIMARY FSGS

Renin-angiotensin blockade
BP control
Statins

IMMUNOSUPPRESSION

Corticosteroids
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Cyclosporine

NEWER IMMUNOSUPPRESSIVES

Tacrolimus
Mycophenolate
TREATMENT OF PRIMARY FSGS

Renin-angiotensin blockade
BP control
Statins

IMMUNOSUPPRESSION

Corticosteroids
Cyclophosphamide
Cyclosporine

NEWER IMMUNOSUPPRESSIVES

Tacrolimus
Mycophenolate

Plasma exchange
Plasma adsorption
CORTICOSTEROIDS IN FSGS

Evidence from randomised controlled trials…
CORTICOSTEROIDS IN FSGS

No RCTs - retrospective cohort studies

1980’s

8 weeks oral prednisolone ~ 1mg/kg/day  [based on MCNS in children]

Complete remission ~ 20-30%
CORTICOSTEROIDS IN FSGS

No RCTs - retrospective cohort studies

1980’s
8 weeks oral prednisolone ~ 1mg/kg/day [based on MCNS in children]
Complete remission ~ 20-30%

1990’s
At least 4 months - prednisolone starting 1-2 mg/kg/day
➢ 4 months treatment - complete remission – 50-60%
INTERPRETING RETROSPECTIVE STUDIES OF TREATMENT IN FSGS
INTERPRETING RETROSPECTIVE STUDIES OF TREATMENT IN FSGS

Definitions of response
Definitions of response

Are the demographics typical?
INTERPRETING RETROSPECTIVE STUDIES OF TREATMENT IN FSGS

Definitions of response

Are the demographics typical?

Is the histology defined?
INTERPRETING RETROSPECTIVE STUDIES OF TREATMENT IN FSGS

Definitions of response

Are the demographics typical?

Is the histology defined?

Were causes of secondary FSGS excluded?
INTERPRETING RETROSPECTIVE STUDIES OF TREATMENT IN FSGS

Who got the treatment?

The worst nephrotics

Those considered fit enough to have steroids?

Physician choice/prejudice?
INTERPRETING RETROSPECTIVE STUDIES OF TREATMENT IN FSGS

Any immunosuppressive therapy must add benefit to ‘best supportive therapy’…

BP 125/75
ACE inhibitor ± ARB
Statin

Were these achieved in retrospective studies?
PRIMARY FSGS WITH NEPHROTIC SYNDROME

Does spontaneous remission occur?
## PRIMARY FSGS WITH NEPHROTIC SYNDROME

Does spontaneous remission occur?

<table>
<thead>
<tr>
<th>Location</th>
<th>Remission Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>4-6%</td>
</tr>
<tr>
<td>European study</td>
<td>16%</td>
</tr>
<tr>
<td>UK 5 centre study</td>
<td>23%</td>
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# PRIMARY FSGS

## Remission rates

<table>
<thead>
<tr>
<th></th>
<th>Spontaneous remission</th>
<th>Treatment remission</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional view</td>
<td>5%</td>
<td>20-50%</td>
<td>4 – 10 fold</td>
</tr>
<tr>
<td>UK 5 centre study</td>
<td>23%</td>
<td>65%</td>
<td>&lt; 3 fold</td>
</tr>
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CORTICOSTEROIDS IN FSGS

There are no RCTs ..we rely on retrospective cohort studies

Is a ‘response’ to 6 months of corticosteroids just a spontaneous remission?

Half of all patients with FSGS will receive 6 months of futile corticosteroids

What is acceptable toxicity?
PREDICTING RESPONSE TO CORTICOSTEROIDS IN FSGS

Genetics

• More steroid resistance in Blacks

• Familial FSGS – usually steroid resistant
PREDICTING RESPONSE TO CORTICOSTEROIDS IN FSGS

Histology

Tip lesion – steroid responsive

Collapsing variant – steroid resistant

Number of glomeruli with segmental / global sclerosis

Tubulo-interstitial fibrosis
CYCLOPHOSPHAMIDE IN FSGS

Evidence from randomised controlled trials…
CYCLOSPORINE IN FSGS

ONE randomised controlled trial
## IMMUNOSUPPRESSION IN PRIMARY FSGS

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<th>Initial response to steroids</th>
<th>Cytotoxic therapy</th>
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<tr>
<td></td>
<td>N</td>
<td>Complete remission</td>
<td>Partial remission</td>
<td>No response</td>
</tr>
<tr>
<td>Steroid-responsive</td>
<td>43</td>
<td>22 (51%)</td>
<td>10 (23%)</td>
<td>11 (26%)</td>
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<tr>
<td>Steroid-resistant</td>
<td>185</td>
<td>31 (17%)</td>
<td>27 (15%)</td>
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<tr>
<td>Cyclosporine A therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroid-responsive</td>
<td>15</td>
<td>11 (73%)</td>
<td>1 (7%)</td>
<td>3 (20%)</td>
</tr>
<tr>
<td>Steroid-resistant</td>
<td>281</td>
<td>82 (29%)</td>
<td>61 (22%)</td>
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Korbet S et al. KI 2002; 62: 2301
## IMMUNOSUPPRESSION IN PRIMARY FSGS

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Korbet S et al. KI 2002; 62: 2301
Female, born 1955 – Primary FSGS
TACROLIMUS IN PRIMARY FSGS
Anecdotal evidence only

MYCOPHENOLATE IN PRIMARY FSGS
Anecdotal evidence only

SIROLIMUS IN PRIMARY FSGS
Anecdotal evidence only
PLASMA EXCHANGE IN FSGS

PRIMARY FSGS

Evidence base is small

~ 20 patients - < 50% have some response
PLASMA EXCHANGE IN FSGS

PRIMARY FSGS

Evidence base is small

~ 20 patients - < 50% have some response

TRANSPLANT RECURRENCE OF PRIMARY FSGS

~ 50% respond. Often completely
TREATMENT OF MEMBRANOUS NEPHROPATHY

- Idiopathic
- Secondary
TREATMENT OF MEMBRANOUS NEPHROPATHY

- Idiopathic
- Secondary
TREATMENT OF MEMBRANOUS NEPHROPATHY

Idiopathic

Secondary

Nephrotic

Non-nephrotic proteinuria
TREATMENT OF MEMBRANOUS NEPHROPATHY

- Idiopathic
  - Nephrotic
- Secondary
  - Non-nephrotic proteinuria
TREATMENT GOALS
IN IDIOPATHIC MEMBRANOUS NEPHROPATHY

Complete or partial remission of proteinuria

Avoid ESRD

Avoid death
VALUE OF PARTIAL REMISSION IN IDIOPATHIC MEMBRANOUS NEPHROPATHY

TORONTO GN REGISTRY - 343 patients

Survival free from renal failure

<table>
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<tr>
<th>Years</th>
<th>CR</th>
<th>PR</th>
<th>NR</th>
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<tr>
<td>0</td>
<td>102</td>
<td>135</td>
<td>106</td>
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<td>67</td>
<td>74</td>
<td>34</td>
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<td>2</td>
<td>33</td>
<td>32</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>9</td>
<td>4</td>
</tr>
</tbody>
</table>

P < 0.001
NR < PR < CR

Troyanov S et al. KI 2004; 66: 1199
10 YEAR FOLLOW UP OF ‘PONTICELLI REGIMEN’ FOR IDIOPATHIC MEMBRANOUS NEPHROPATHY WITH NEPHROTIC SYNDROME

Ponticelli C et al. KI 1995; 48: 1600
In 6 months the patient receives:

9 grams Methylprednisolone

And oral Prednisolone 0.4mg/kg/alt day for 3 months

plus

Chlorambucil 0.2 mg/kg/day for 3 months

or

Cyclophosphamide 2.5 mg/kg/day
Outcomes in untreated membranous nephropathy

- **Nephrotic syndrome**
- **Proteinuria**
- **Remission**
- **Death or dialysis**

*Duration of known disease (years)*

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RESTRICTED USE OF IMMUNOSUPPRESSIVE TREATMENT IN IDIOPATHIC MEMBRANOUS NEPHROPATHY

The Nijmegen strategy

Immunosuppression only for deteriorating renal function or intractable nephrotic syndrome

74% 7 year renal survival [32% in historical controls]

Complete or partial remission 86%

IMPACT OF IMMUNOSUPPRESSIVE TREATMENT ON ESRD IN IDIOPATHIC MEMBRANOUS NEPHROPATHY

The Nijmegen strategy
Prednisolone & cyclophosphamide only for declining GFR or intractable nephrotic syndrome

Incidence of ESRD due to IMN: 1991 – 2005

70% reduction in Nijmegen compared to remainder of Netherlands

Hofstra J, Wetzels J et al. NDT 2008 epub 17 July
IMMUNOSUPPRESSIVE TREATMENT FOR IDIOPATHIC MEMBRANOUS NEPHROPATHY IN ADULTS WITH NEPHROTIC SYNDROME

Cochrane Review: 18 trials – 1025 patients

CORTICOSTEROIDS

No beneficial effect on any end point

Schieppati A et al. www.thecochranelibrary.com
IMMUNOSUPPRESSIVE TREATMENT FOR IDIOPATHIC MEMBRANOUS NEPHROPATHY IN ADULTS WITH NEPHROTIC SYNDROME

Cochrane Review: 18 trials – 1025 patients

CYCLOSPORIN

No beneficial effect on any end point

Schieppati A et al. www.thecochranelibrary.com
IMMUNOSUPPRESSIVE TREATMENT
FOR IDIOPATHIC MEMBRANOUS NEPHROPATHY
IN ADULTS WITH NEPHROTIC SYNDROME

Cochrane Review: 18 trials – 1025 patients

ALKYLATING AGENTS

Beneficial effect on complete remission only

Cyclophosphamide – fewer discontinuations for adverse effects than Chlorambucil

Schieppati A et al. www.thecochranelibrary.com
PROGNOSIS OF UNTREATED PATIENTS WITH IDIOPATHIC MEMBRANOUS NEPHROPATHY

100 ‘consecutive’ patients

BP Rx / diuretics as indicated

Some ACE inhibitors

BP defined >160/95

Schieppati A et al. NEJM 1993; 329: 85
PROGNOSIS OF UNTREATED PATIENTS WITH IDIOPATHIC MEMBRANOUS NEPHROPATHY

Schieppati A et al. NEJM 1993; 329: 85
PROGNOSIS OF IDIOPATHIC MEMBRANOUS NEPHROPATHY IN JAPAN

949 patients followed for 20 years
No RCTs

374 corticosteroids
257 alkylating agents
157 other immunosuppressives
161 ‘supportive therapy

Shiiki H et al. Kidney Int 2004; 5: 1400
Blood pressure defined as > 160/90

Renin-angiotensin blockade?
IMMUNOSUPPRESSIVE TREATMENT FOR IDIOPATHIC MEMBRANOUS NEPHROPATHY IN ADULTS WITH NEPHROTIC SYNDROME

Cochrane Review: 18 trials – 1025 patients

POSSIBLE CONFOUNDING FACTORS

Use of ACE inhibitors/ARB - ? no effect

BP control – no data

Schieppati A et al. www.thecochranelibrary.com
Tight BP control
125/75

Full renin-angiotensin blockade

Statin
Tight BP control
125/75

Full renin-angiotensin blockade

Statin
Tight BP control
125/75

Full renin-angiotensin blockade

Statin

Deteriorating renal function or intractable nephrotic syndrome
Tight BP control
125/75

Full renin-angiotensin blockade

Statin

Deteriorating renal function or intractable nephrotic syndrome

What is the evidence that immunosuppressive regimens give additional benefit?
MYCOPHENOLATE IN RESISTANT MEMBRANOUS NEPHROPATHY

4 SMALL ‘PILOT’ STUDIES – total 80 patients

MMF 2g/day for 6-16 months

Proteinuria reduced in 3 of 4 studies

No effect on renal function

Miller G et al. AJKD 2000; 36: 250
Polenakovic M et al. NDT 2003; 18: 1235
Chan TM et al. Nephrology 2007; 12: 576
Dussol B et al. AJKD 2008 epub 26 June
RITUXIMAB

Anti-CD20 monoclonal antibody

Two doses typically depletes peripheral B cells for 4-6 months

? FcγRIII polymorphisms modify B cell response

Safety profile encouraging
RITUXIMAB IN IDIOPATHIC MEMBRANOUS NEPHROPATHY

8 patients
Proteinuria > 3.5g/day for 6 months before Rx

Rituximab – 4 weekly infusions

BP ‘controlled’

Full dose ACE inhibitor

Ruggenenti P et al. JASN 2003; 14: 1851
RITUXIMAB
IN IDIOPATHIC MEMBRANOUS NEPHROPATHY

8 patients
Proteinuria > 3.5g/day for 6 months before Rx

Rituximab – 4 weekly infusions

Repeat biopsy in 7 patients
Partial reabsorption of subepithelial deposits
Increase in slit diaphragms
Reduced IgG4 staining

Ruggenenti P et al. JASN 2003; 14: 1851
N = 14 - mean proteinuria 10.8 g/day despite BP control & RAS blockade

Rituximab – 1g x 3 over 6 months

2 complete remissions
6 partial remissions

Responsiveness *not* predictable

Fervenza FC *et al.* Kidney Int 2008; 73: 117
ECULIZAMAB [C5 COMPLEMENT INHIBITOR] IN MEMBRANOUS NEPHROPATHY

RCT

No effect on proteinuria or renal function

Incomplete complement inhibition

Appel G et al. JASN 2002; 13: 668A
MEMBRANOPROLIFERATIVE / MESANGIOCAPILLARY GLOMERULONEPHRITIS
MEMBRANOPROLIFERATIVE / MESANGIOCAPILLARY GLOMERULONEPHRITIS
CLASSIFICATION OF GLOMERULONEPHRITIS

Histopathology

Patterns established on light microscopy
- Membranous
- Mesangiocapillary
- Focal segmental glomerulosclerosis
  
  *etc*......

Clinical

Immune mechanisms

‘Patterns’ not ‘diseases’
AETIOLOGY OF MESANGIOCAPILLARY GN

Infection
- Hepatitis B & C
- Bacterial endocarditis
- Infected shunt/abscess
- HIV
- Hantavirus

Malignancy
- CLL
- Lymphoma

Auto-immune disease
- Lupus
- Sjogren syndrome
- Cryoglobulinaemia (HCV)

Inherited or acquired complement deficiency
AETIOLOGY OF MESANGIOCAPILLARY GN

Infection
- Hepatitis B & C
- Bacterial endocarditis
- Infected shunt/abscess
- HIV
- Hantavirus

Malignancy
- CLL
- Lymphoma

Auto-immune disease
- Lupus
- Sjogren syndrome
- Cryoglobulinaemia (HCV)

Inherited or acquired complement deficiency

“IDIOPATHIC“
MESANGIOCAPILLARY GN TYPE II

Only identified as a separate entity when EM became available

‘Dense deposit disease’
MESANGIOCAPILLARY GN

53 children presenting 1980 - 2000 Birmingham & Bristol, UK

31 Type 1
14 Type 2
2 Type 3

Cansick JC et al. NDT 2004; 19: 2769
DENSE DEPOSIT DISEASE

LIGHT MICROSCOPY

Mesangiocapillary 25%
Mesangial proliferative 45%
Crescentic 18%

Transplant recurrence 100%

Characteristic alternative pathway complement activation

Walker P et al. 2007
COMPLEMENT ACTIVATION IN DENSE DEPOSIT DISEASE

C3 NEPHRITIC FACTOR
A stabilising autoantibody against C3 convertase

PERSISTENT C3 ACTIVATION
COMPLEMENT ACTIVATION IN DENSE DEPOSIT DISEASE

C3 NEPHRITIC FACTOR
A stabilising autoantibody against C3 convertase

PERSISTENT C3 ACTIVATION

Associated with partial lipodystrophy
COMPLEMENT ACTIVATION IN DENSE DEPOSIT DISEASE

C3 NEPHRITIC FACTOR
A stabilising autoantibody against C3 convertase

COMPLEMENT FACTOR H
Loss of function mutations

PERSISTENT C3 ACTIVATION
Stabilised by C3Nef

Loss of function factor H mutations

Deplete Plasma exchange Rituximab

Replace Plasma infusion

Block Anti-C5Ab
CLASSIFICATION OF GLOMERULONEPHRITIS

- Histopathology
- Clinical
- Immune mechanisms
TREATMENT OF MESANGIOCAPILLARY GN

Very few RCTs

Most are > 20 years old

Cohorts include MCGN I of many aetiologies

And may include dense deposit disease
TREATMENT OF GLOMERULAR DISEASE PATTERNS

Do the simple things properly
Minimise adverse effects of treatment
Wait for evidence
Help create the evidence
TREATMENT OF GN ASSOCIATED WITH EXTRARENAL IMMUNE DISEASE

- Goodpasture’s disease
- Lupus
- Systemic vasculitis
GOODPASTURE’S DISEASE – ANTI-GBM DISEASE

A rare condition studied in great detail...

Expecting that general principles will emerge about auto-immunity and self-tolerance which will improve treatment of all types of GN
TREATMENT OF GOODPASTURE’S DISEASE

1980

Prednisolone
Cyclophosphamide
Plasma exchange
TREATMENT OF GOODPASTURE’S DISEASE

2008

Prednisolone
Cyclophosphamide
Plasma exchange
PROBLEMS IN THE TREATMENT OF LUPUS NEPHRITIS
QUESTION:

How do you get ten different opinions about the treatment of lupus nephritis?
QUESTION:
How do you get ten different opinions about the treatment of lupus nephritis?

ANSWER:
Ask nine different nephrologists
LUPUS NEPHRITIS

The archetypal ‘immune complex’ disease

Glomerular immune deposits

... although the antigens involved in the complexes remain incompletely defined

Highly variable expression of renal disease
PROBLEMS IN THE TREATMENT OF LUPUS NEPHRITIS

The evidence base is small
PROBLEMS IN THE TREATMENT OF LUPUS NEPHRITIS

There are few Randomised Controlled Trials

Nearly all are trials in ‘Proliferative’ (III & IV) lupus nephritis

Most studies use histological entry criteria

Most studies include only previously untreated patients

Most studies exclude severely ill patients
PROBLEMS IN THE TREATMENT OF LUPUS NEPHRITIS

Little evidence about….

Mild disease

Very severe disease

Prolonged relapsing disease
PROBLEMS IN THE TREATMENT OF LUPUS NEPHRITIS

The ‘precious’ patient

Seeing beyond the kidneys
THE EVIDENCE BASE FOR TREATMENT OF LUPUS NEPHRITIS

WHO Class I & II  No trials

WHO Class III & IV  Many reports

but

Fewer RCTs than most people think

... and some are from a different era

WHO Class V  One small RCT
Lupus causes premature mortality
... even without renal failure

Infection

Cardiovascular disease

including premature atherosclerosis
TREATMENT DECISIONS IN LUPUS NEPHRITIS

Base a treatment decision on *all* of the following:

- Renal histology
- Extent of clinical renal disease
- Extrarenal lupus
- Serology
- Previous treatment
TREATMENT FOR WHO III & IV ‘PROLIFERATIVE’ LUPUS NEPHRITIS

**Induction treatment**

**Maintenance treatment**
TREATMENT OF WHO III & IV LUPUS NEPHRITIS

META-ANALYSIS

There is very strong evidence that corticosteroids plus a cytotoxic agent gives superior outcome to corticosteroids alone.
META-ANALYSIS

There is very strong evidence that corticosteroids plus a cytotoxic agent gives superior outcome to corticosteroids alone.

...... but which cytotoxic agent?
TREATMENT FOR WHO III & IV LUPUS NEPHRITIS

Induction treatment

Most physicians accept that ....

Cyclophosphamide is more potent and allows more rapid control of severe disease
TREATMENT FOR WHO III & IV LUPUS NEPHRITIS

Induction treatment

Most physicians accept that ....

Cyclophosphamide is more potent and allows more rapid control of severe disease

But does that mean all patients require cyclophosphamide?
TREATMENT OF WHO III & IV LUPUS NEPHRITIS

Is cyclophosphamide better than azathioprine?

Is IV cyclophosphamide better than oral?

How much cyclophosphamide is required?

Is mycophenolate good enough?
TREATMENT OF WHO III & IV LUPUS NEPHRITIS

Is cyclophosphamide better than azathioprine?

Is IV cyclophosphamide better than oral?

How much cyclophosphamide is required?

Is mycophenololate good enough?
**TREATMENT OF DIFFUSE PROLIFERATIVE LUPUS NEPHRITIS**

Meta-analysis – Cochrane methodology

### Cyclophosphamide or azathioprine + steroids vs steroids alone

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Weight</th>
<th>RR (random) 95% CI</th>
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<td>Donadio 1978</td>
<td>4/24</td>
<td>6/26</td>
<td>18.23</td>
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<td>Austin 1986</td>
<td>5/38</td>
<td>5/14</td>
<td>20.30</td>
<td>0.37 [0.13, 1.08]</td>
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<td>Boumpas 1992</td>
<td>7/40</td>
<td>6/25</td>
<td>25.09</td>
<td>0.73 [0.28, 1.92]</td>
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<td>Sesso 1994</td>
<td>2/14</td>
<td>3/15</td>
<td>8.82</td>
<td>0.71 [0.14, 3.66]</td>
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<td>Gourley 1996</td>
<td>9/55</td>
<td>6/27</td>
<td>27.56</td>
<td>0.74 [0.29, 1.86]</td>
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<td>Subtotal (95% CI)</td>
<td>171</td>
<td>107</td>
<td>100.00</td>
<td>0.63 [0.39, 1.03]</td>
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<td>Total events: 27 (Treatment), 26 (Control)</td>
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<tr>
<td>Test for heterogeneity: $\chi^2 = 1.23, df = 4 (P = 0.87)$, $I^2 = 0%$</td>
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<td>Test for overall effect: $Z = 1.84 (P = 0.07)$</td>
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</table>

<table>
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<tr>
<th>Study or sub-category</th>
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<th>Control n/N</th>
<th>Weight</th>
<th>RR (random) 95% CI</th>
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<tr>
<td>Azeithioprine</td>
<td>2/13</td>
<td>7/15</td>
<td>47.26</td>
<td>0.33 [0.08, 1.32]</td>
</tr>
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<td>Austin 1986</td>
<td>7/19</td>
<td>2/7</td>
<td>52.74</td>
<td>1.29 [0.35, 4.78]</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>32</td>
<td>22</td>
<td>100.00</td>
<td>0.66 [0.17, 2.55]</td>
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<td>Test for heterogeneity: $\chi^2 = 1.99, df = 1 (P = 0.16)$, $I^2 = 49.7%$</td>
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<td>Test for overall effect: $Z = 0.60 (P = 0.55)$</td>
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</table>

*AJKD 2004; 43:197*
NIH DATA ON CYTOTOXIC AGENTS IN PROLIFERATIVE LUPUS NEPHRITIS

Steinberg A et al  Arth Rheum 1991; 34: 945
There has never been

a head-to-head comparison of

Cyclophosphamide and azathioprine

in an RCT
There has never been a head-to-head comparison of Cyclophosphamide and azathioprine in an RCT
INDUCTION and MAINTENANCE THERAPY IN PROLIFERATIVE LUPUS NEPHRITIS

CYCLOPHOSPHAMIDE vs AZATHIOPRINE

RCT n = 87 WHO III & IV

IV cyclophosphamide for 3 years + oral prednisolone

Vs

Oral azathioprine for 3 years + oral prednisolone + initial IV methylprednisolone

Ligtenberg G et al ASN abstract 2002
INDUCTION and MAINTENANCE THERAPY IN PROLIFERATIVE LUPUS NEPHRITIS

CYCLOPHOSPHAMIDE vs AZATHIOPRINE

RCT n = 87

Interim analysis at 32 months

No difference in renal outcome

Herpes zoster increased with cyclophosphamide

No other differences in adverse events

Ligtenberg G et al ASN abstract 2002
TREATMENT OF WHO III & IV LUPUS NEPHRITIS

Is cyclophosphamide better than azathioprine?

Is IV cyclophosphamide better than oral?

How much cyclophosphamide is required?

Is mycophenolate good enough?
TREATMENT OF WHO III & IV LUPUS NEPHRITIS

Is cyclophosphamide better than azathioprine?

Is IV cyclophosphamide better than oral?

How much cyclophosphamide is required?

Is mycophenolate good enough?
TREATMENT OF WHO III & IV LUPUS NEPHRITIS

Is IV cyclophosphamide better than oral?

High intermittent dosing may improve therapeutic index

May reduce cytopenias and infections

May assist compliance
TREATMENT OF WHO III & IV LUPUS NEPHRITIS

Is IV cyclophosphamide better than oral?

There are no RCTs
TREATMENT OF WHO III & IV LUPUS NEPHRITIS

Is cyclophosphamide better than azathioprine?

Is IV cyclophosphamide better than oral?

How much cyclophosphamide is required?

Is mycophenolate good enough?
NIH Study

Maintenance quarterly IV cyclophosphamide is superior to short induction treatment

... but this was compared to steroid only maintenance treatment

LOW DOSE VERSUS HIGH DOSE CYCLOPHOSPHAMIDE IN PROLIFERATIVE LUPUS NEPHRITIS

‘Eurolupus Nephritis Trial’- RCT

90 patients – median follow up 41 months

HIGH DOSE CYCLOPHOSPHAMIDE

6 monthly + 2 quarterly pulses
Initial dose 500mg/m2
Dose increased according to WCC nadir
Mean total dose 8.5 gm

LOW DOSE CYCLOPHOSPHAMIDE

6 monthly pulses of 500mg
Total dose 3 gm

Followed by
AZATHIOPRINE 2mg/kg/day for 30 months

Houssiau et al Arth Rheum 2002; 46: 2121
LOW DOSE VERSUS HIGH DOSE CYCLOPHOSPHAMIDE IN PROLIFERATIVE LUPUS NEPHRITIS

‘Eurolupus Nephritis Trial’- RCT

No difference between high and low dose cyclophosphamide in:

- Achieved renal remission [~80%]
- Renal flares during follow up [28%]
- Severe infection [2-fold increase with high dose-NS]

Houssiau et al. Arth Rheum 2002; 46: 2121
ETHNICITY & LUPUS NEPHRITIS

Lupus nephritis is more common and more severe in some racial groups including -

African Americans
Hispanics
South Asians
South East Asians

NIH studies: ~40% African Americans

European studies: White Caucasians
TREATMENT OF WHO III & IV LUPUS NEPHRITIS

Is cyclophosphamide better than azathioprine?

Is IV cyclophosphamide better than oral?

How much cyclophosphamide is required?

Is mycophenolate good enough?
Diffuse proliferative lupus nephritis
RCT – within 48 hours of biopsy

- Mycophenolate 2g/day
- Mycophenolate 1g/day
- Azathioprine 1.5mg/kg/day
- Cyclophosphamide 2.5mg/kg/day
- Azathioprine 1.5mg/kg/day
- Azathioprine 1.5mg/kg/day

Months:
- 0
- 6
- 12
- 18

Chan; NEJM 2000; 343: 1156
MYCOPTHENOLATE IN PROLIFERATIVE LUPUS NEPHRITIS

Chan TM et al JASN 2005; 16: 1076

Number of patients
30  27  24  22  15  9  4  CTX-AZA
32  20  18  14  11  7  4  MMF

Proportion of patients without relapse (%)

Time after remission (month)

P=0.3
Mycophenolate in Proliferative Lupus Nephritis

N = 46 - 6 months – open label prospective trial

Mycophenolate vs ‘pulse’ cyclophosphamide

At 6 months

Mycophenolate

Greater reduction in proteinuria and haematuria

Greater reduction in anti-dsDNA antibodies

More improvement in glomerular inflammation [repeat biopsies in 30]

Mycophenolate [up to 3g/day] vs ‘pulse’ cyclophosphamide

At 6 months

Mycophenolate

Superior response rate 67 vs 47% p=0.007
Cross over to other regimen less common
Fewer serious infections

Ginzler EM et al – Arth Rheum 2003; 48: S647
Mycophenolate has mostly been studied as an induction agent.

There is some evidence about its use and acceptability as a maintenance agent.
MAINTENANCE IMMUNOSUPPRESSIVE THERAPY IN PROLIFERATIVE LUPUS NEPHRITIS

RCT n = 59       Miami

All received induction therapy with cyclophosphamide

THEN for maintenance therapy..

Randomised

‘Pulse’ cyclophosphamide  Azathioprine  Mycophenolate

Contreras G et al  NEJM 2004; 350:971
Patient survival **not** different

**ADVERSE EFFECTS**

- Cyclophosphamide > Azathioprine or mycophenolate
- Hospitalisations
- Amenorrhoea
- Infections

Contreras G *et al*  NEJM 2004; 350:971
MAINTENANCE IMMUNOSUPPRESSIVE THERAPY IN PROLIFERATIVE LUPUS NEPHRITIS

EVENT FREE SURVIVAL – death or double serum creatinine

Contreras G et al. NEJM 2004; 350:971
MAINTENANCE IMMUNOSUPPRESSIVE THERAPY IN PROLIFERATIVE LUPUS NEPHRITIS

RELAPSE FREE SURVIVAL

Contreras G et al NEJM 2004; 350:971
MAINTENANCE IMMUNOSUPPRESSIVE THERAPY
IN PROLIFERATIVE LUPUS NEPHRITIS

Because of the relative toxicity of cyclophosphamide

It is only necessary to prove equivalence
for azathioprine or mycophenolate

Given the cost
it is only necessary to prove equivalence
between azathioprine and mycophenolate
OTHER TREATMENTS FOR LUPUS NEPHRITIS

Calcineurin inhibitors

Sirolimus

Total lymphoid irradiation

Anti-CD40 ligand antibody

Rituximab

Abetimus

etc....
OTHER TREATMENTS FOR LUPUS NEPHRITIS

Calcineurin inhibitors

The evidence for all these is anecdotal

Anti-CD40 ligand antibody

Rituximab

Abetimus

e tc....
OTHER TREATMENTS FOR LUPUS NEPHRITIS

Calcineurin inhibitors

Sirolimus

Total lymphoid irradiation

Anti-CD40 ligand antibody

Rituximab

Abetimus

etc....
RITUXIMAB IN LUPUS NEPHRITIS

6 studies

96 patients [64 nephritis]

Some response in all patients

Complete remission ~ 40%

Includes some patients resistant to cyclophosphamide

Walsh M, Jayne D. Kidney Int 2008; 72: 676
COURSE OF LUPUS NEPHRITIS AFTER RESPONSE TO INDUCTION THERAPY

145 patients received induction treatment with ‘pulse’ cyclophosphamide and methylprednisolone

Of those with complete or partial response.....

45% had at least one nephritic flare during 10 years follow up

9/11 who reached ESRD had severe nephritic flares

Illei G et al  Arth Rheum 2002; 46: 995
COURSE OF LUPUS NEPHRITIS AFTER RESPONSE TO INDUCTION THERAPY

Euro-Lupus Nephritis Trial

Remission at 6 months

is the best predictor of long term outcome

Houssiau F et al Arth Rheum 2004; 50: 3934
DIAGNOSIS OF RENAL FLARES IN LUPUS

Proteinuria persisting or increasing during treatment

Activity or chronicity?

Increase immunosuppression

Or

Renin-angiotensin blockade

Or

Both?
It is always a pleasure to take credit
for a therapeutic manoeuvre
in a patient with lupus...
It is always a pleasure to take credit for a therapeutic manoeuvre in a patient with lupus…

...when all you are doing is observing spontaneous improvement
COMMON THERAPEUTIC ERRORS IN LUPUS NEPHRITIS

Toxicity because high dose induction treatment for too long

Flares because stop maintenance too early

Activity not distinguished from chronicity
TREATMENT FOR PROLIFERATIVE LUPUS NEPHRITIS

What do I do?

INDUCTION

Prednisolone + azathioprine unless fulminant disease

If no response
Mycophenolate [or cyclophosphamide]
TREATMENT FOR
PROLIFERATIVE LUPUS NEPHRITIS

What do I do?

MAINTENANCE

Low dose prednisolone + azathioprine

…. for a very long time
PERSONAL PRINCIPLES FOR THE MANAGEMENT OF LUPUS NEPHRITIS

‘Never kill the patient to save the kidneys’

People with lupus have the right not to look Cushingoid

Fertility must be respected

Maximise objective evidence about disease activity

Never forget lupus is an unpredictable disease
GLOMERULONEPHRITIS ASSOCIATED WITH SMALL VESSEL VASCULITIS

‘Pauci-immune’

Is ANCA directly pathogenic?
Circulating antineutrophil cytoplasmic antibodies (ANCA) with paucity of vascular IF immunoglobulin staining.

- No asthma or granulomas: Microscopic polyangiitis
- Granulomas and no asthma: Wegener’s granulomatosis
- Eosinophilia, asthma, and granulomas: Churg-Strauss syndrome
TREATMENT OF SMALL VESSEL SYSTEMIC VASCULITIS

Treatment is effective

75% 5 year kidney survival

Better outcome if treat earlier
TREATMENT OF SMALL VESSEL SYSTEMIC VASCULITIS

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INDUCTION - Corticosteroids plus Cyclophosphamide

Effective *but* toxic
TREATMENT OF SMALL VESSEL SYSTEMIC VASCULITIS

We have very little evidence about treatment of relapsing disease.

Most evidence is about induction and maintenance of first remission.
TREATMENT OF SMALL VESSEL SYSTEMIC VASCULITIS

Specific therapeutic questions

‘Pulse’ or oral cyclophosphamide ?
Methylprednisolone or plasma exchange for severe disease ?
Azathioprine or cyclophosphamide for maintenance therapy ?
Specific therapeutic questions

‘Pulse’ or oral cyclophosphamide?

Methylprednisolone or plasma exchange for severe disease?

Azathioprine or cyclophosphamide for maintenance therapy?

Before the mid-1990’s there were no available RCT’s
EUVAS

The European Vasculitis Study Group

Founded 1993

First trial started recruiting 1996

First trial published 2003
TREATMENT OF SMALL VESSEL SYSTEMIC VASCULITIS

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CYCLOPHOSPHAMIDE IN ANCA-POSITIVE VASCULITIS
Oral or IV Pulse?

Meta-analysis of 3 RCTs [154 patients] and 11 non-RCTs

Limited data……

Pulse therapy → More remissions
Less leucopenia
Fewer infections
More relapses

No difference in ESRD or death

d de Groot NDT 2001; 17: 2018
CYCLOPS – a EUVAS TRIAL

Daily oral versus pulse cyclophosphamide for induction therapy in renal vasculitis

No difference in remission or relapse rates

Total dose halved using pulse regimen

Unpublished data
TREATMENT OF
SMALL VESSEL SYSTEMIC VASCULITIS

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Azathioprine or cyclophosphamide for maintenance therapy?
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CYCAZAREM

Randomised trial of cyclophosphamide versus azathioprine during remission in ANCA-associated systemic vasculitis

European Vasculitis Study Group (EUVAS)

143 patients randomised from 11 countries
Remission therapy with azathioprine is equally effective to cyclophosphamide and probably safer.

Adverse-effects are frequent and severe - 26%
TREATMENT OF SMALL VESSEL SYSTEMIC VASCULITIS

‘Pulse’ or oral cyclophosphamide?
Azathioprine or cyclophosphamide for maintenance therapy?
Methylprednisolone or plasma exchange for severe disease?
Biopsy-proven ANCA-associated necrotizing GN with creatinine >500µmol/l

151 patients from 9 European countries

7 PE treatments (each of 60ml/kg) within the first two weeks

or

3 ‘pulses’ of ivMeP (15mg/kg)

+ oral cyclophosphamide and prednisolone

European Vasculitis Study Group
Renal outcome at 3 months significantly better with Plasma Exchange
dialysis-free survival (p=0.017)
Difference most marked in patients requiring dialysis at presentation
RITUXIMAB IN RENAL VASCULITIS

7 published reports
62 patients [35 nephritis]

Mostly added to conventional therapy or ‘rescue’

73% complete remission
RITUXIMAB IN RENAL VASCULITIS

Unanswered questions ....

Dosing regimen?

Long term adverse effects?

Effective in induction + conventional Rx?

Impact on relapse rate?

Two RCTs of induction therapy are underway

Walsh M, Jayne D. Kidney Int 2008; 72: 676
EUVAS

European Vasculitis Study Group

A major success

conducting RCTs which were thought near impossible

Ongoing trials include -
EUVAS - ONGOING TRIALS

Long-term low dose immunosuppression versus treatment withdrawal for renal vasculitis

Mycophenolate or azathioprine for remission therapy in renal vasculitis

Rituximab as induction therapy