Lupus Nephritis in Children

Carmine Pecoraro

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Children Hospital “Santobono”
Napoli, Italy
I declare that I have no conflict of interest

Carmine Pecoraro
Systemic Lupus Erythematosus

• The prototype of the complex and polyedric autoimmune diseases
• A wide spectrum of clinical manifestations and abnormal immuneresponses.; Especially, production of autoantibodies to nuclear antigens, cell surfaces and serum proteins
• **Kidney** is one of the main target organs
1997 Update of the 1982 American College of Rheumatology revised criteria for classification of systemic lupus erythematosus

1. **Malar rash** – a rash over the cheeks and nose, often in the shape of a butterfly
2. **Discoid rash** – a rash that appears as red, raised, disk-shaped patches
3. **Photosensitivity** – a reaction to sun or light that causes a skin rash to appear or get worse
4. **Oral ulcers** – sores appearing in the mouth
5. **Arthritis** – joint pain and swelling of two or more joints in which the bones around the joints do not become destroyed
6. **Serositis** – inflammation of the lining around the lungs (pleuritis) or inflammation of the lining around the heart that causes chest pain which is worse with deep breathing (pericarditis)
7. **Kidney disorder** – persistent protein or cellular casts in the urine
8. **Neurological disorder** – seizures or psychosis
9. **Blood disorder** – anemia (low red blood cell count), leukopenia (low white blood cell count), lymphopenia (low level of specific white blood cells), or thrombocytopenia (low platelet count)
10. **Immunologic disorder** – anti-DNA or anti-Sm or positive antiphospholipid antibodies
11. **Abnormal antinuclear antibody (ANA)**

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SLICC Classification Criteria for Systemic Lupus Erythematosus

Requirements: ≥ 4 criteria (at least 1 clinical and 1 laboratory criteria) OR biopsy-proven lupus nephritis with positive ANA or Anti-DNA

Clinical Criteria

1. Acute Cutaneous Lupus*
2. Chronic Cutaneous Lupus*
3. Oral or nasal ulcers *
4. Non-scarring alopecia
5. Arthritis *
6. Serositis *
7. Renal *
8. Neurologic *
9. Hemolytic anemia
10. Leukopenia *
11. Thrombocytopenia (<100,000/mm³)

Immunologic Criteria

1. ANA
2. Anti-DNA
3. Anti-Sm
4. Antiphospholipid Ab *
5. Low complement (C3, C4, CH50)
6. Direct Coombs’ test (do not count in the presence of hemolytic anemia)

†SLICC: Systemic Lupus International Collaborating Clinics
* See notes for criteria details

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OUTLINE OF PRESENTATION

• Epidemiology
• Clinical Presentation
• Histopathological Classification
• Treatment
• Prognosis
• Conclusions
# Lupus Nephritis in Children: Series

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<td>2009</td>
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<td>95</td>
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*Italian Collaborative Study*
LUPUS NEPHROPATHY IN CHILDREN: AGE AT ONSET AND SEX

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Systemic Lupus Erythematosus

- Mean age at diagnosis: 10-12 yrs
- Female/Male: 7 / 1
- 10-15% onset < 16 yrs age
- 85% Pediatric SLE: diagnosis ≥ 8 yrs
- Incidence: 0.5-0.6 100,000 p.p.
- Prevalence: 5-6 per 100,000 p.p.
OUTLINE OF PRESENTATION

• Epidemiology
• Clinical Presentation
• Histopathological Classification
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• Conclusions
OUTLINE OF PRESENTATION

• Clinical Presentation
Clinical Presentation

General Statement

Presenting Symptoms of SLE are frequently protean in children and many patients begin the disease with a limited number of ACR criteria and may therefore not be diagnosed as having SLE after the first symptoms.

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Clinical Manifestations at onset in children with SLE in Pediatric Nephrology Settings: i.e.: Genua and Naples
Pediatric SLE: clinical characteristics

Childhood-Onset versus Adult-Onset

• More severe disease onset

• Higher frequency of Fever and systemic symptoms

• Higher frequency of Hematological Signs

• Higher frequency of Renal Involvement

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Hematological Symptoms: THROMBOCYTOPENIA

**Immune Thrombocytopenia secondary to SLE**

- ✓ 161/539 pts (29.9%)  
  Wang F, Lupus 1997
- ✓ 134/1000 pts (13.4%)  
  Cervera R, Medicine 2003

**“IDIOPATHIC” Thrombocytopenic Purpura as First Sign of future SLE**

- ✓ 1997: 5%  
  Mestanza-Peralta M, J Reumatol 1997
- ✓ 1999: 8%  
  Balsalobre AJ, An Med Interna 1999
- ✓ 2006: 5%  
  C. Pecoraro
RAZIONALE DELLO STUDIO

We evaluated, retrospectively, our children with Lupus Nephritis in whom First Sign was Thrombocytopenic Purpura, initially considered as “IDIOPATHIC”.

No data on “ITP” as First Sign in Children who will develop Nephritis secondary to SLE

Are these subjects at Higher Risk to develop SLE Nephritis

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Characteristics of Children with Lupus Nephritis

✓ 50 pts with Lupus Nephritis
✓ 45 F/5 M (mean age 12.2 anni)

Renal Signs at LN onset

<table>
<thead>
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<th>Renal Signs</th>
<th>Patients (%)</th>
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<tr>
<td>Proteinuria</td>
<td>100</td>
</tr>
<tr>
<td>Micr. Hematuria</td>
<td>95</td>
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<tr>
<td>Macr. Hematuria</td>
<td>70</td>
</tr>
<tr>
<td>Nephrot. Sindr</td>
<td>50</td>
</tr>
<tr>
<td>ARF</td>
<td>20</td>
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<tr>
<td>Hypertension</td>
<td>10</td>
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</table>
11/50 (22%) LN pts had ITP as unique sign at onset

- 11 Pts (F:M= 10:1)
- ANA positive at ITP onset : 6/11

Mean age: ITP versus SLE onset

\[\Delta = 4.2 \text{ yrs}\]
CONCLUSIVE REMARKS

“IDIOPATHIC” Thrombocytopenic Purpura as First Sign of future SLE:
• Hazzan R, Pediatr Blood Cancer 2006: 5%
• Manna A, Pecoraro C, 2011: 22%

Female Sex
ANA +
Chronic ITP

Associated Risk Factors

In Children “ITP” as First Sign of SLE could be a predictive Risk Factor for future LUPUS NEPHRITIS

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Pediatric SLE: clinical characteristics

RENAL INVOLVEMENT: 50-75%

- Hematuria
- Proteinuria
- Nephritic Syndrome
- Nephrotic Syndrome
- Rapid Progressive GN
“Full House” Urine Sediment at Microscopic Examination
Case Definition for LN as per ACR criteria

- Persistent proteinuria : \( \geq 0.5 \text{g/day or Uprot/Ucreat } \geq 0.5 \) or 3+ dipstick
- Glomerular Hematuria
- Casts: cellular, granular, red blood cells
- Renal Biopsy : immune complex mediated GN compatible with LN

A Renal Biopsy should be performed for any suspicion of GN
“Full House” Nephropathy

**Full-House Nephropathy** is defined by the detection of a “Full house” immunofluorescence pattern on renal biopsy without the simultaneous clinical and serological signs and symptoms of SLE, so called “**LUPUS sine LUPUS**”
Revision of Immunofluorescence pattern of 243 renal biopsies

“F-H“ I.F. was diagnosed, according to the literature, when more than trace amounts of Ig and C were present in renal glomeruli. Diagnostic criteria required prevalence of IgG, presence of IgA and/or IgM and both C1q and C3

49 Full-House IF (20%)

Medical Records

22 pts
Clinical&Serological SLE

27 pts
NO Signs of SLE

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27 Pts with Full House Nephropathy

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<tr>
<th></th>
<th>18 males</th>
<th>9 females</th>
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<tr>
<td><strong>Mean age:</strong></td>
<td>11.8 years (5.6-16.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Mean onset age:</strong></td>
<td>7.3 years (3.2-15.4)</td>
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**CLINICAL ONSET**

19/27 Nephrotic Syndrome ± Hematuria
3/27 Non-Nephrotic Proteinuria ± Hemat.
1/27 HUS
1/27 ARF
3/27 ANS

*All have had a follow-up >1 year.
*All pts had received renal biopsy within 6 months from disease onset.

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7/27 Pts (26%) developed **Clinical and/or Serologic signs of SLE** after a mean time of 2.4 years (0.8-5.8) from disease onset

<table>
<thead>
<tr>
<th>Pt</th>
<th>SLE signs</th>
<th>Time(years)</th>
<th>Pt</th>
<th>SLE signs</th>
<th>Time(years)</th>
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<tbody>
<tr>
<td>1</td>
<td>AntidsDNA/malar rash</td>
<td>2.3</td>
<td>5.</td>
<td>$\downarrow$ C3 and C4</td>
<td>0.8</td>
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<tr>
<td>2</td>
<td>ANA pos / $\downarrow$ C3</td>
<td>1.0</td>
<td>6.</td>
<td>$\downarrow$ C3 and C4</td>
<td>1.6</td>
</tr>
<tr>
<td>3</td>
<td>ANA and AMA pos</td>
<td>5.8</td>
<td>7.</td>
<td>$\downarrow$ C3 and C4, ANA pos</td>
<td>2.9</td>
</tr>
<tr>
<td>4</td>
<td>ANA POS/malar rash</td>
<td>2.1</td>
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OUTLINE OF PRESENTATION

• Histopathological Classification
The primary clinical purposes for a pathologic classification system are to:

Facilitate communication:
  Between pathologists
  Between pathologists and clinicians
  Between clinicians
  In understanding the literature

Facilitate clinical management:
  Guiding treatment
  Suggesting proposals
  Indicating an etiology or pathogenic mechanism
Pathologic Classification Of Lupus Nephritis

“Original WHO Classification”
Buffalo, NY, 1974; or Geneva, 1975

“Modified WHO Classification”
ISKDC, Paris, 1980 (Churg and Sobin, 1982)

“Modified WHO Classification”
Churg 1995

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Copyright Jan J. Weening
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% or > glomeruli)
Class V  Membranous LGN
Class VI Advanced sclerotic LGN (>90% sclerotic glomeruli)

* for classes III and IV, the diagnosis should include one of the following: with active lesions/with active and chronic lesions/ inactive with scars
* for classes III and IV, the diagnosis should include the percentage of glomeruli with fibrinoid necrosis or cellular crescents when present
* for class IV, the diagnosis should include one of the following: predominantly segmental (IV-S)/predominantly global (IV-G)
* class V may occur in combination with III or IV in which case both will be diagnosed
Class IV-G A/C and Class V
OUTLINE OF PRESENTATION

• Treatment

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• Optimal treatment of Lupus Nephritis is still a Challenge because of the heterogeneity of the disease at onset and of the unpredictable course.
THERAPEUTIC GOALS OF THE “IDEAL” TREATMENT

- Rapid Remission
- To avoid Flares
- To avoid Chronic Renal Failure
- Minimal toxic side effects (mainly in children)
SURVIVAL RATE OF CHILDREN WITH SLE NEPHRITIS

• Before modern therapies: 50% after 2 yrs (Zetterstrom, *Acta Ped*, 1956)
• Steroids + Cycloph. and Aza: 90% after 10 yrs (Cameron, *Pediatr Nephrol*, 1996)
• 2000 yrs: 90 % after 15 yrs (Hagelberg, *J Rheumatol*, 2002)

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A look into the Past ........

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Survival in patients with lupus nephritis.
Pollak V et al J Lab Clin Med 63,537, 1964
Disadvantages of Steroid Monotherapy

• Need of high doses
• High morbidity
• High mortality
• High incidence of “flares”
• High incidence of Steroid toxicity

• The association of immunosuppressant drugs improves therapeutic index

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A pooled analysis of RCT comparing immuno-suppressive drugs + prednisone vs prednisone alone in lupus nephritis

Felson D, Anderson J. NEJM 311,1528,1984

• Less renal function deterioration $p=0.0006$
• Less end-stage renal failure $p=0.02$
• Death $p= \text{ns}$

Adverse renal events (vs prednisone alone)

• Cyclophosphamide + prednisone - 40%
• Azathioprine + prednisone - 40%

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Low-dose versus High-dose i.v. cyclophosphamide Euro-Lupus Nephritis Trial

Houssiau et al. Arthritis and Rheum. 2002

Induction therapy 1 MP pulse 750mg for 3 days of IV

**High-dose CYC**
- 8 monthly IV CYC pulses (1g)
- Mean 8.5±1.9 gr
- Azathioprine 2mg/Kg/day from 13th to 30th month

**Low dose CYC**
- 6 every 2 weeks CYC 500mg
- Total 3 g
- Azathioprine 2mg/Kg/day from the 4th to the 30th month.

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## EURO-LUPUS NEPHRITIS TRIAL
Long Lerm follow-up
*Houssiau et al Arthritis and Rheum. 2004*

<table>
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<tr>
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<th>High-dose CYC 45 pts</th>
<th>Low-dose CYC 44 pts</th>
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<tbody>
<tr>
<td>Renal failure</td>
<td>6.6%</td>
<td>9.0%</td>
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<tr>
<td>Death</td>
<td>0</td>
<td>4.5%</td>
</tr>
<tr>
<td>Renal flares</td>
<td>29%</td>
<td>26%</td>
</tr>
<tr>
<td>Renal remission</td>
<td>54%</td>
<td>70%</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>20%</td>
<td>16%</td>
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<tr>
<td>Severe infection</td>
<td>22%</td>
<td>11%</td>
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NOW!

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Assuming that class I/II do not require immunesuppressive drugs

Therapeutic Strategy for LN

1. INDUCTION
   First 6 months

2. MAINTENANCE

ACR Recommendations

Dooley MA. Lupus 2004, 13: 857
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INDUCTION

MAINTENANCE

MMF 2-3 g/d × 6 mo (preferred to CYC in Hispanics and African American) plus GC pulse × 3 d then prednisolone 0.5-1.0 mg/kg per day, tapered after a few weeks to lowest effective dose (1 mg/kg per day if crescent seen)

or

CYC plus GC pulse × 3 d then prednisolone 0.5-1 mg/kg per day, tapered after a few weeks to lowest effective dose (1 mg/kg per day if crescent seen)

Low dose CYC 500 mg i.v. every 2 wk × 6 mo Followed by maintenance with oral MMF or AZA (White European)

or

High dose CYC 500-1000 mg/m² BSA i.v. every month × 6

Improved

Not improved

MMF 1-2 g/d or AZA 2 mg/kg per day +/- low dose daily GC

CYC (low/high) + pulse GC then daily GC

MMF 1-2 g/d or AZA 2 mg/kg per day +/- low dose daily GC

Maintenance MMF 1-2 g/d or AZA 2 mg/kg per day +/- low dose daily GC

Rituximab or calcineurin inhibitors + GC

Improved

Not improved

MMF 1-2 g/d or AZA 2 mg/kg per day +/- low dose daily GC

Maintenance MMF 1-2 g/d or AZA 2 mg/kg per day +/- low dose daily GC

Rituximab or calcineurin inhibitors + GC

Not improved

Rituximab or calcineurin inhibitors + GC
WHICH THE BEST THERAPY OF PROLIFERATIVE LUPUS NEPHRITIS?

• STEROIDS
• AZATIOPRINE
• CICLOPHOSPHAMIDE PULSES I.V.
• MOFETIL MICOPHENOLATE
• CALCINEURIN INHIBITORS

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TREATMENT OF CHILDHOOD LUPUS NEPHRITIS (LN) WITH MYCOPHENOLATE MOFETIL (MMF): CLINICAL AND HISTOPATHOLOGICAL STUDY.

F. Nuzzi, D. Molino, G. Malgieri, MR. D’Armiento, C. Pecoraro

Unit of Nephrology and Dialysis
Santobono Children Hospital
Naples, Italy
LITERATURE EVIDENCES

Adults : Controlled Trials

- **Zhu B et al**: MMF in Induction and Maintenance therapy of severe LN: a meta-analysis of RCTs. *NDT 2007 Jul*
- **Appel GB et al**: MMF vs CyP for induction treatment of LN (ASPREVA) *J Am Soc Nephrol 2009*
- **Kamanamool N et al**: Efficacy and adverse events of MMF vs CyP for induction therapy of LN. Review and meta-analysis. *Medicine 2010*

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LITERATURE EVIDENCES
Children : No Controlled Trials

• Saskin E. Use of low dose CyP followed by AZA/MMF treatment in childhood LN. *Pediatr Nephrol* 2009

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MMF vs iv Cyp for induction treatment of LN

N=370 - Class III, IV, V

Mycophenolate mofetil target 3g/die
Intravenous cyclophosphamide 0.5-1 g/mq in boli mensili

Dopo 24 settimane:
Remissione completa
MMF 8.6%
CF ev 8.1%

Appel G B et al. JASN 2009
MMF vs AZA as maintenance therapy for LN

227 cases, follow up 36 months

MMF 2 g/die
AZA 2 mg/kg/die

No. at Risk
Mycophenolate mofetil
Azathioprine

A

Probability of Being Free of Treatment Failure

Months

P = 0.003

B

Probability of Being Free of Renal Flare

Months

P = 0.03

No. at Risk
Mycophenolate mofetil
Azathioprine


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AZA vs MMF as maintenance therapy for LN
(Euro-Lupus trial)

105 casi
MMF 2 g/die
AZA 2 mg/kg/die

Free of renal flare (%)

HR MMF: 0.75 [0.33-1.71]

MMF [48] [47] [43] [40] [34] [34] [22] [24] [15] [18]
AZA

Houssiau, Ann Rheum Dis 2010

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AIM OF THE STUDY

To evaluate the risk/benefit profile of MMF in *inducing and maintaining remission* in children with Lupus Nephritis
PATIENTS AND METHODS

*63 children (57F/6M, mean age 12.2 yrs) affected by SLE, according ARA Criteria

*53 pts (81%) kidney involvement;

*41/53 treated with MMF to Induce and Maintain remission of Lupuis Nephritis

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### Characteristics of 41 children with LN treated with MMF

<table>
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<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Number of patients</td>
<td>41</td>
</tr>
<tr>
<td>Mean Age at onset of LN, yrs</td>
<td>12.7 range: 5-19.9</td>
</tr>
<tr>
<td>F/M Ratio</td>
<td>7/1</td>
</tr>
<tr>
<td>LN first sign of SLE N° Pts.</td>
<td>31 (75%)</td>
</tr>
<tr>
<td>LN after 3.8 yrs mean period medio from SLE onset (range 1-11 anni), Number of patients</td>
<td>10 (25%)</td>
</tr>
</tbody>
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Renal Manifestations at onset of LN in children treated with MMF

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Pathological Classification (Weening), Kidney Biopsy performed in 39 pts before MMF therapy start

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MMF Treatment Protocol

3 MP I.V. Pulses /on alternate days, then P 2 mg/kg/day/os plus MMF os, mean dose 29 ± 7.7 mg/kg/day

Treatment before MMF IN 4 PZ with Flare up: 28 newl diagnosis

• CICLOPHOSPHAMIDE i.v.: 2 Pts
• AZA: 1 Pt; AZA + CsA: 1 Pt; .

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FOLLOW-UP

• Proteinuria;
• Renal Function;
• SLE Serological Markers (C3);
• Kidney Biopsy (10 pts).
• Therapy variations
• Side Effects

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24h Proteinuria at 4.5 yrs (0.5-7.3) mean follow-up

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Renal Function (pCr) in 9 Pts with renal failure at onset

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RESULTS

- C3 Normalized: 25/41 (61%)

- Steroid decalage after 4.6 ± months: 15/41 (36.5%);

- Steroid maintainance 0.3 mg/kg/os alternate days: 27/39 (69.5%);

- Proteinuric Flares: increase of P: 10/39 (26%);

- Off Therapy from 1.7 yrs (0.8-3.2) after at least 4 yrs therapy, no flares from at least 3 yrs, proteinuria < 1 g, normal pCreat, inactive urinary sedimento: 6/41 (14.7%)

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<th>I KB</th>
<th>II KB</th>
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<td>2 C.A.</td>
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<td>8 N.T.</td>
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<td>9 A.C.</td>
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</table>
SIDE EFFECTS

- Gastrointestinal symptoms - shift to gastroresistant formula: $6/41$ (14.5%);

- MMF temporary stopped because of H. Zoster: $2/41$ (4.8%);

- Hair defluvium: $9/41$ (18.5%);

- No hematological side effects: $41/41$ (100%).

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CONCLUSIONS

• MMF represents an useful option to traditional therapies of LN in children. MMF can achieve, also as unique drug, a good disease control without significant side effects

• In selected cases we can withdraw any treatment

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Calcineurin Inhibitors: are they useful in LN?

Tacrolimus for Induction Therapy of LN

<table>
<thead>
<tr>
<th>Autore</th>
<th>N</th>
<th>BR</th>
<th>Terapia</th>
<th>Durata (anni)</th>
<th>Clinica</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen (1998)</td>
<td>81</td>
<td>III-IV-V</td>
<td>TAC 42 CF 39</td>
<td>0.6</td>
<td>remissione TAC 52.4% CF 38.5%</td>
</tr>
<tr>
<td>Wang (2012)</td>
<td>40</td>
<td>IV-V</td>
<td>TAC 20 CF 20</td>
<td>1</td>
<td>remissione TAC 75% CF 40%</td>
</tr>
<tr>
<td>Li (2013)</td>
<td>60</td>
<td>III-IV-V</td>
<td>TAC 20 MMF 20 CF 20</td>
<td>0.6</td>
<td>remissione TAC 45% MMF 40% CF 30%</td>
</tr>
<tr>
<td>Cortes-H (2010)</td>
<td>70</td>
<td>III-IV-V</td>
<td>Induzione MMF Aggiunto TAC in 17pz</td>
<td>2</td>
<td>miglioramento protu remissione 70%</td>
</tr>
<tr>
<td>Fei (2013)</td>
<td>26</td>
<td>III-IV-V</td>
<td>Induzione con CF Aggiunto TAC in 26pz</td>
<td>0.6</td>
<td>remissione parziale o completa 88.5%</td>
</tr>
</tbody>
</table>

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MMF + TAC + PN for induction treatment of Class V + IV LN

40 casi (20+20) Classe V+IV

Cumulative probability of complete remission

Follow up (months)

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Bao H et al. JASN 2008
PN, Cyp and CyA in lupus membranous nephropathy (induction therapy)

Gehan
$P = 0.002$, CSA vs. Pred
$P = 0.04$, IVCY vs. Pred

No. at Risk
CSA  12  9  7  5  4  3  3
IVCY  15 14 11  9  7  6  6
Pred  15 15 15 13 11 11 11

Gehan, $P = 0.02$

No. at Risk
CSA  10  5  2
IVCY  9  7  6  4  2  2

Austin et al  JASN 2009

42 casi
RITUXIMAB

• Several, but anecdotal cases of severe SLE treated successfully
• Review 2006 by Thatayatikom on Autoimmunity Rev
• Dose: 375 mg/m2/week x 2 o 4 times
• Complete B-depletion from 1 to 3 months
• No B-deplezione, No clinical response
• B-depletion lasting 3 -12 months, clinical improvement lasts more time

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RITUXIMAB

• No so defined beneficial effects on Lupus Nephritis
• 33/45 N (classe III e IV) response evaluated by scores (SLEDAI)
• pCreat e Uprot: Not omogeneous results
• Difficulty in evaluation of effectiveness because og clinical heterogeneity, differente doses aand associatde drugs
• Effective in controlling many SLE symptoms
• RCTs are needed to confirm its role in Lupus Nephritis

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RITUXIMAB

• **French Pediatric-onset SLE Study Group:** Rituximab Therapy for childhood-onset Lupus Erythematosus. *J Pediatr* 2006 May

• **El-Hallak M et al:** Clinical effects and safety of Rituximab for treatment of refractory pediatric autoimmune diseases. *J Pediatr* 2007 Apr

• **Moroni G:** rituximab monotherapy for remission induction of proliferative nephritis flares. *J Nephrol.* 2010 May-Jun

• **Roccatello D:** Intensive short term treatment with rituximab, cyclop. and methylprednis. induces remission and avoids further immunosuppressive maintenance therapy. *NDT 2011, Mar* C.Pecoraro
RITUXIMAB

- **EXPLORER study**: *Arthritis Rheum* (2010): NO difference between Rtx e Plac in extrarenal lupus 237 pts

- **LUNAR trial**: Int. Congress on SLE, Vancouver (2010): NO significant difference between Rtx e plac. In 144 ptz

- No significant side effects in both studies

- Rituximab as rescue therapy in children resistant to standard therapy
A look to the Future

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New Developments in the Treatment of Systemic Lupus Erythematosus

Kjell Tullus.

Great Ormond Street Hospital for Children, London

Pediatr Nephrol, published online 26 April 2011

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• OCRELIZUMAB: fully humanized Ab anti CD 20. BELONG study (Vancouver 2010): no risultati, sembra gravi infezioni

• BELIMUMAB: fully humanized Ab anti soluble BLy-S (stimulator) o BAFF (factor) citochina che stimola i B linfo. Due studi: BLISS-52 (865 pz)e BLISS-76 (449 pz), no published

• EPRATUZUMAB (anti CD22), ABETIMUS (induce tolleranza di B linfo verso dsDNA)

• IFLIXIMAB, ABATACEPT, RIGEROMID

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Ranchin B., Fargue S.

Organization of international registries and controlled trials in children with lupus nephritis is mandatory to determine long term prognosis and to validate less toxic therapy regimens in childhood.

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OUTLINE OF PRESENTATION

• Prognosis
Factors of poor prognosis of Lupus Nephritis

- Male Sex
- Young age
- Black people
- Increase of Creatinine
- Nephrotic Proteinuria
- Activity Indexes
- Chronicity Indexes
- No Compliance with Therapy
- Social status
Predictive Factors to Doubling Creatinine Anemia at Onset

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Predictive factors to doubling Creatinine
Anti Phospholipid Antibodies

Moroni G et al Am J Kidney Dis 43,28,2004

% 100
90
80
70
60
50
40
30
20
10
0

0 50 100 150 200 250

Months

NO Antiphospholipid Ab

AntiPhospholipid Ab.

P = 0.02

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Renal Flares (0.22/pz/anno)

Nephritic Flares
Rapid Increase of creatinine > 30% vs basal Creatinine + Nephritic Urinary Sediment

Proteinuric Flares
Increase of proteinuria at least 2 g/die

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Probability of Doubling Creatinine

Moroni G et al. Kidney Int 1996

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Proteinuric flares

Nephritic flares

P = 0.00001

Probability of doubling Creatinine

Moroni G et al. Kidney Int 1996
LUPUS NEPHRITIS in children: 5 YEARS SURVIVAL

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Relapse-free survival.
Can we stop the therapy in children with LN?

<table>
<thead>
<tr>
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<th>N</th>
<th>F up anni</th>
<th>Recidive</th>
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<tbody>
<tr>
<td><strong>Pablos 1994</strong></td>
<td>11/11</td>
<td>6.4</td>
<td>36%</td>
</tr>
<tr>
<td><strong>Mosca 2002</strong></td>
<td>33/75</td>
<td>4</td>
<td>45%</td>
</tr>
<tr>
<td><strong>Moroni 2006</strong></td>
<td>32/102</td>
<td>3</td>
<td>53%</td>
</tr>
</tbody>
</table>

After STOPPING

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Conclusions 1

- Early and aggressive treatment improves prognosis
- Complete remission is the goal to guarantee a better prognosis
- Conventional Therapy is always of value
- MMF is effective in induction as in maintenance therapy
Conclusions 2

- Calcineurin Inhibitors are to consider in Induction too
- Younger children who do not achieve complete remission are at risk of poor prognosis and need for a more and prolonged therapy
- Withdrawal of therapy is still debated and may be considered only in few cases

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THANK YOU
CLINICAL CASE & Questions

Pablo Picasso, “Pesca di notte a Antibes” (1939)
2013 February (12 years):
Microscopic Hematuria and Proteinuria

1 year before:
Fever and rash
Synovitis: ankle; wrists
Treated with PDN and HCl

Greta

BMI: 90°pc

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Is it possible to make the diagnosis of SLE?

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SLICC\(^\d\) Classification Criteria for Systemic Lupus Erythematosus

Requirements: \(\geq 4\) criteria (at least 1 clinical and 1 laboratory criteria)
OR biopsy-proven lupus nephritis with positive ANA or Anti-DNA

Clinical Criteria

1. Acute Cutaneous Lupus
2. Chronic Cutaneous Lupus
3. Oral or nasal ulcers
4. Non-scarring alopecia
5. Arthritis
6. Serositis
7. Renal
8. Neurologic
9. Hemolytic anemia
10. Leukopenia
11. Thrombocytopenia (<100,000/mm\(^3\))

Immuneologic Criteria

1. ANA
2. Anti-DNA
3. Anti-Sm
4. Antiphospholipid Ab
5. Low complement (C3, C4, CH50)
6. Direct Coombs’ test (do not count in the presence of hemolytic anemia)

Laboratory tests:
- High levels of liver enzymes
- **Leukopenia** (WBC 2900/mmc)
- **Low** C3 and C4
- Negative Direct Coombs
- **ANA** >1:1280; **anti-dsDNA** 1911 UI/ml

\(\dagger\) SLICC: Systemic Lupus International Collaborating Clinics

* See notes for criteria details
Renal biopsy….Which pathologic class?

Proliferative Diffuse Glomerulonephritis. Epitelial Crescents in 25-50% of glomeruli, with diffuse subendothelial immune deposits, with slight mesangial alterations.

IF: predominantly mesangial and subendothelial immune deposits of IgG, IgM, C3 and C1q.

A. Class I/II
B. Class III C
C. Class IV
D. Class VI

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What kind of treatment for Greta?

PTU mg/24 h

- PDN+HC

Options:
- A. Aza+PDN
- B. MMF+PDN
- C. Rituximab +PDN
- A. Aza+MMF+PDN
- B. PDN+HC+MMF

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On follow-up…

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And now what therapy for Greta?

<table>
<thead>
<tr>
<th>Date</th>
<th>PTU mg/24 h</th>
<th>Creatinine mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>February 2012</td>
<td>PDN+HC</td>
<td>C3 0.5 g/L, C4 0.07 g/L</td>
</tr>
<tr>
<td>May 2013</td>
<td>PDN+MMF</td>
<td>C3 0.57 g/L, C4 0.06 g/L</td>
</tr>
<tr>
<td>September 2013</td>
<td>PDN+MMF</td>
<td>C3 0.5 g/L, C4 0.07 g/L</td>
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<tr>
<td>October 2013</td>
<td>PDN+MMF</td>
<td>C3 0.57 g/L, C4 0.06 g/L</td>
</tr>
<tr>
<td>November 2013</td>
<td>PDN+MMF</td>
<td>C3 0.5 g/L, C4 0.07 g/L</td>
</tr>
<tr>
<td>December 2013</td>
<td>PDN+MMF</td>
<td>C3 0.57 g/L, C4 0.06 g/L</td>
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</table>

A. Rituximab +PDN  
B. Aza+PDN  
C. Aza+MMF+PDN  
D. PDN+HC+MMF  
E. Other

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