The Role of Cyclosporine A in the Treatment of Nephrotic Syndrome

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Cyclosporine A

- Another alternative to steroids
- Safety and tolerability
- Side effects
  - Hypertrichosis 18%
  - Gum hyperpasia 16%
  - Gastrointestinal symptoms 11%
  - Hypertension 9%
  - Nephrotoxicity

CyA in Minimal Change

- Pediatrics: regression of cushingoid features and catch-up growth
- Adults: disappearance of steroid-induced diabetes and cause of hip osteonecrosis
- Stopping treatment almost constantly followed by relapse- cyclosporin dependency
- Success rate in steroid-resistant forms: only 20 - 30%
- Failure of CyA : no remission within 4 months

Frequent Relapser or Steroid Dependency

1. Short course of cyclophosphamide or chlorambucil (8-12 weeks)
2. Alternate day prednisone minimal dose - hypercorticism sign
3. Switch to CsA - remission - dose reduction after 6-12 months to minimal effective dose
4. Gradually stop CsA after 2 years

Is CsA dependency inevitable(I) ?

- Stopping CsA within the first year of successful treatment usually leads to relapse of NS - major concern
- Long-term follow-up of 36 adult cases since 1985 in France (Meyrier et al. 1994)
  - 14 cases treated with CsA for 26+14.5m(12-60) and tapered to a stop

CsA Dependency(II)

- Remained in remission in 11 without steroids and 3 with low dose of steroid and escaped from CsA dependency for 9m to 6 year
- This indicates that CsA responder are not inescapably destined to exposure to this drug

Long-term tolerance of CsA

1) Treatment of MCD with normal renal function with CsA less than 5.5 mg/dk/day is safe and efficient
2) FSGS with pre-existing incipient renal insufficiency and tubulointerstitial lesions - relatively hazardous
3) Repeat biopsy after 1 year of treatment is necessary to stop or continue
4) Prolonged remission for more than 1 year with CsA can induce stable remission

Focal and Segmental Glomerulosclerosis

- Most nephrotic patients progress to ESRD within 10 years after clinical onset
- Tubulointerstitial lesions - a bad renal prognosis
- Prognostic role of glomerular lesions: hilar lesions, mesangial proliferation and collapsing glomeruli - unclear

Cyclosporine in FSGS

- Effective in both steroid-dependent and steroid-resistant FSGS.
- Partial or complete remission mostly likely in steroid-dependent type while the response rate in steroid-resistant disease has 20-70%.
- One possible contributing factor is a cyclosporine-cholesterol interaction, higher than conventional doses (up to 10-14 mg/kg) may be required when the plasma cholesterol concenteration is above 350-400 mg/dl.

Aggressive long-term CsA therapy for FSGS

Tejani A et al. J Am Soc Nephrol 1995, 5:1820

- To investigate whether long-term CsA therapy in steroid-resistant FSGS will prevent progression to ESRD
  - CsA 6 mg/kg/day for 27.5(3-97)m in 21 children and follow-up 8.5+4.7 yr
  - Mean proteinuria fell from 6.2+0.2 to 2.0+0.1/24h and albumin rose from 1.95+0.04 to 3.41+0.04 g/dl
- ESRD rate: 5/21(24%), vs. historical patients 42/54(78%)

Prognostic Factors in FSGS

- The degree of proteinuria
- The degree of renal dysfunction
- The response to therapy

Cyclosporine A in Steroid Resistant Idiopathic Nephrotic Syndrome

Niaudet, P et al. J Pediatr 1994;125;981.

- 65 children with steroid-resistant nephrosis were treated with cyclosporine in combination with prednisone(30 mg/m^2 per day for one month followed by alternate day prednisone for five months).
- Complete remission in 42%(48% with MCD, 30% with FSGS)- one half remitted within 1 month.
- 8/27 responders became steroid-sensitive with subsequent relapses and non of the responders progressed to ESRD.

Is success predictable in a given patient ?

- Previous steroid response is best predictive of remission, irrespective of glomerular lesions(i.e., MCD or FSGS)
- Some steroid-resistant FSGS or MCD
  - no reliable criteria to anticipate
- High risk of treatment failure
  - FSGS with tubulointerstitial lesions and incipient renal insufficiency

Membranous Nephropathy

Natural history of untreated patients with MGN

- Spontaneous remission of proteinuria
  : 5 - 20%
- Partial remission(< 2 g of proteinuria per day)
  : 25-40%
- The incidence of ESRD
  : 4% at 5 years, 35% at 10 years,
  41% at 15 years

Immunosuppressive Therapy in MGN

- Alternating monthly prednosone(0.5 mg/kg per day) and chlorambucil(0.2 mg/kg per day) for a total 6 months. The steroid months begun with pulse methylprednisolone 1g iv for 3 days.
- Low-dose cyclophosphamide(1.5 mg/kg per day) plus alternate-day prednisone(60-100mg q.o.d.).
- Cyclophosphamide(1.5 mg/kg per day) for 6 months plus warfarin and dipyridamole for 2 years.

Long-term cyclosporin A therapy for severe idiopathic membranous nephropathy.

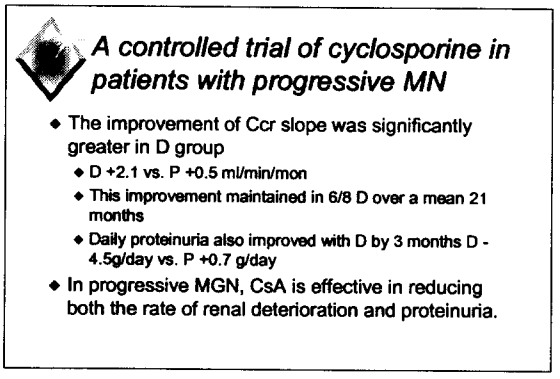
Guy Rostoker et al. Nephron 1993: 63;335

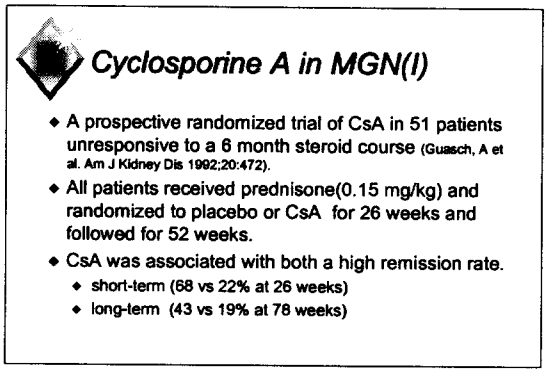
- 15MN with indicators of poor prognosis(proteinuria greater than 10 g/day)
- 4/15 nephrotic patients with MN
  treated with CsA for 15 months (12-30) entered complete remission and another 7 had partial remission— 11/15 (73%)
- 3/9 relapse on withdrawal but remained sensitive to CsA
- CsA may be efficient in treatment of MN

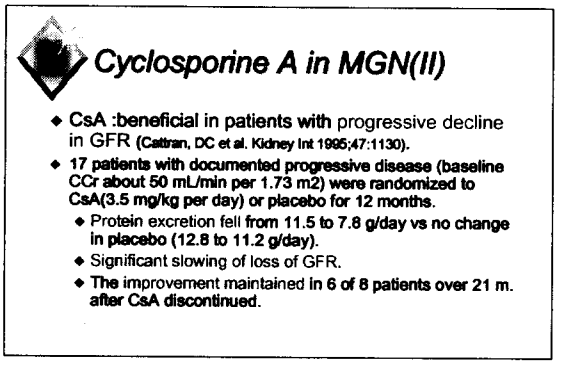
A controlled trial of cyclosporine in patients with progressive MN

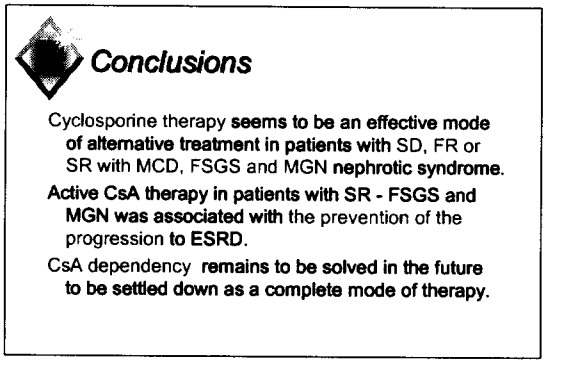
Cattran et al. Kidney Int 47, 1995

- 64 MN on a restricted protein diet (<0.9 g/kg) for 12 m - part I
- Patients at high risk of prgression
  absolute loss of creatinine clearance of >8ml/min and persistent nephrotic proteinuria : D (N=9) or P (N=8) for 12 m - part 2









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