Rituximab or Cyclosporine in the Treatment of Membranous Nephropathy

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ORIGINAL ARTICLE

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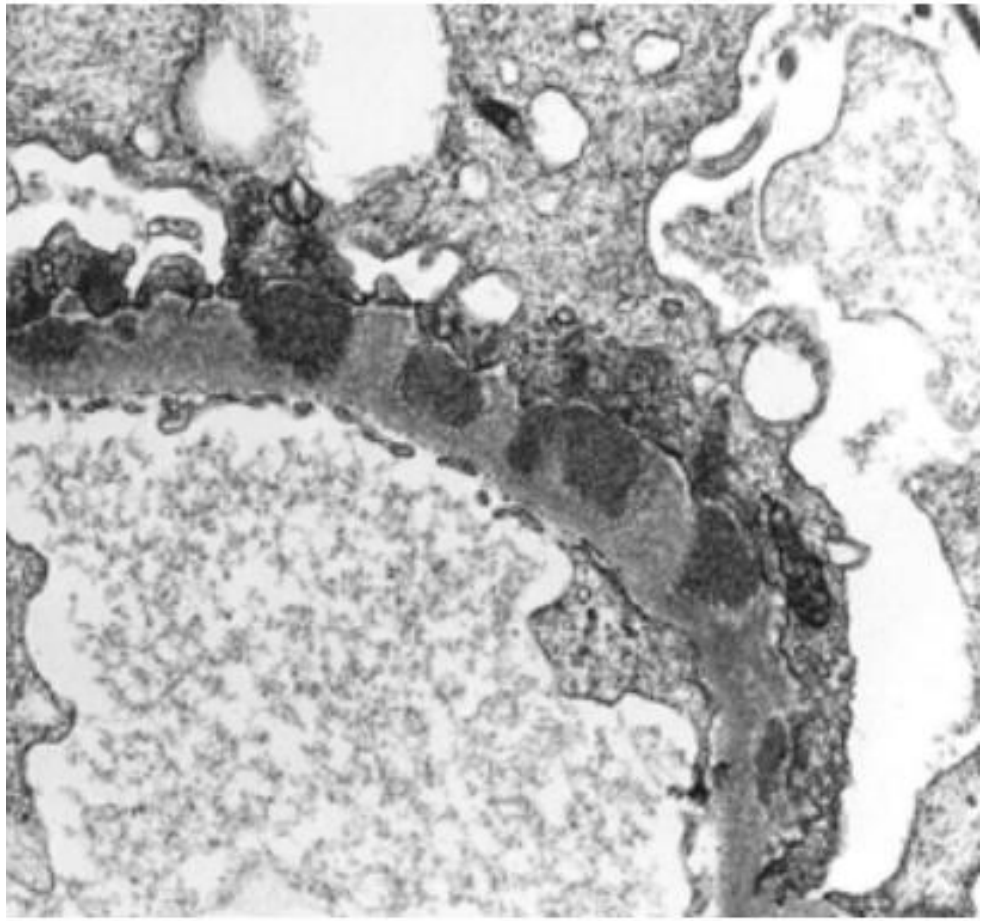
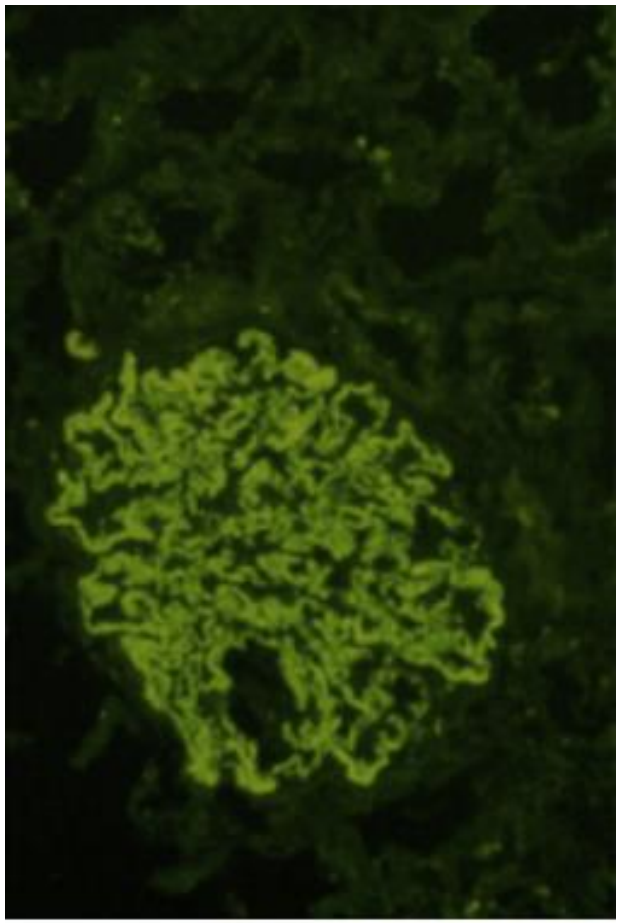
Introduction - Membranous Nephropathy

- Leading cause of nephrotic syndrome in adults
- Approximate incidence among white adults without diabetes, 8 to 10 cases per million population per year
- 2:1 Male predominance
- The result of IgG and complement deposition along the glomerular basement membranes
- Commonest presentation is with nephrotic syndrome. Small proportion present with sub-nephrotic proteinuria or ESRF
- Immune complexes form against anti-PLA2R or anti-THSD7A antibodies

Introduction - Membranous Nephropathy





Introduction - Current Treatment

- First line
  - RAAS blockade
  - Diuretics
  - Control of hyperlipidaemia
- If persistent nephrotic range proteinuria immunosuppression required
  - Glucocorticoid monotherapy not effective
  - High remission rates with calcineurin inhibitors
  - Cyclophosphamide ± steroids often used

Evidence for Rituximab in Membranous Nephropathy

- Rationale: Targeting CD20 on B cells causing a reduction in mature B-cell proliferation with reduced production of anti-PLA2R and anti-THSD7A antibodies
- First reported use in 2002 in 8 patients
- GEMRITUX study found rituximab reduced circulating anti-PLA2R levels but trial underpowered for clinical outcomes with only 6 month follow up
- A lower anti-PLA2R level has been associated with lower rates of progression of membranous nephropathy

Methods – Trial Design

- Open-label, randomized, multicenter, noninferiority trial
- 22 sites in North America
- Genentech (the manufacturers of rituximab) financially supported the trial and provided trial medication but was not involved in trial design or data analysis

Methods - Participants

- Eligibility criteria
  - Biopsy confirmed membranous nephropathy
    - (biopsy samples centrally reviewed as part of trial protocol)
  - 18-80 years of age
  - Proteinuria of >5g/24 hours on 2 24 hour collections within 14 days
  - Have a decline of less than 50% in proteinuria despite renin– angiotensin system blockade for at least 3 months before randomization
  - Stable quantified 24-hour creatinine clearance of at least 40 ml per minute per 1.73 m2 of body-surface area
  - If female, not pregnant; if not post-menopausal or surgically sterile, must be practicing medically approved contraceptive method
  - Not exposed to prednisone or mycophenolate mofetil for > 1 month, not exposed to alkylating agents for > 6 months

Methods - Interventions

- For 3 months prior to randomisation
  - RAA blockade
  - Blood-pressure management targeting a value of less than 130/80 mmHg
  - Dietary sodium restriction to less than 4 g per day
  - Dietary protein restriction to 0.8 to 1 g of protein per kilogram of body weight per day

Methods - Interventions

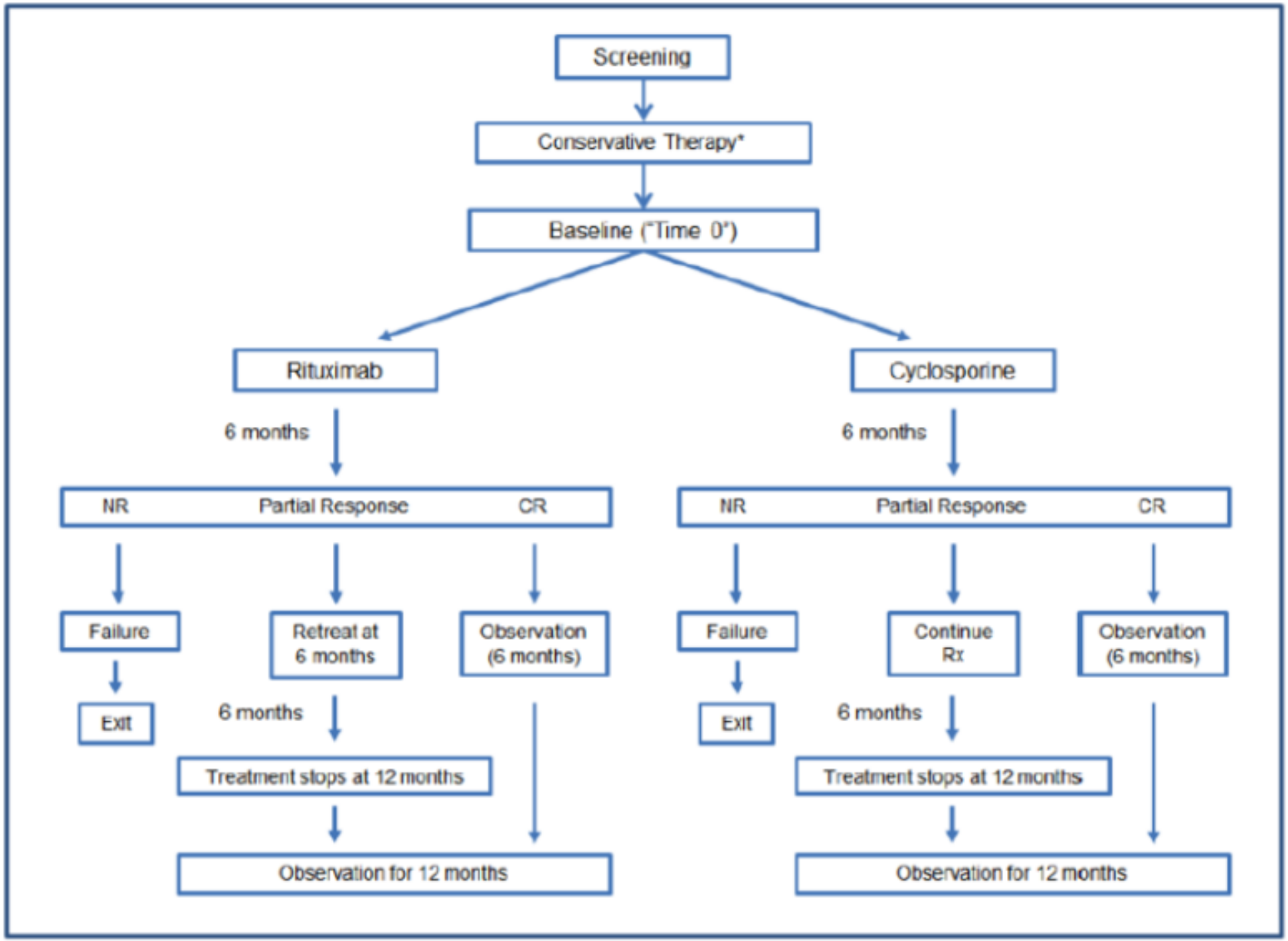
- Patients who were assigned to the rituximab group received
  - 1000 mg of intravenous medication (Rituxan, Genentech) on days 1 and 15.
  - If proteinuria was reduced from baseline by at least 25% at 6 months but there was not complete remission, a second course of rituximab was administered regardless of the CD19+ B-cell count.
  - If complete remission was observed at 6 months, no second course was given.
  - If proteinuria was reduced by less than 25% by 6 months, the patient was considered to have treatment failure and no further rituximab was administered

Methods - Interventions

- Patients who were assignd to the cyclophosphamide group received
  - Oral dose of 3.5 mg per kilogram per day, divided into two equal doses given at 12-hour intervals.
  - Target trough blood levels of cyclosporine were 125 to 175 ng per milliliter.
  - Blood levels were assessed every 2 weeks until the target trough level was reached.
  - If complete remission was observed at 6 months, cyclosporine was tapered and discontinued over a 2-month period.
  - If proteinuria was reduced from baseline by less than 25% at 6 months, the patient was considered to have treatment failure and cyclosporine was discontinued.
  - If proteinuria was reduced by at least 25%, cyclosporine was continued for an additional 6 months. At the end of 12 months, cyclosporine was tapered by one third of the maintenance dose monthly and discontinued after 2 months.

Methods – Outcomes and Follow Up

- Primary clinical outcome:
  - Composite of complete or partial remission at 24 months
- Secondary clinical outcomes:
  - Composite of complete or partial remission at 6, 12, and 18 months
  - Complete remission at 6, 12, 18, and 24 months
  - Time to treatment failure up to 24 months
  - End-stage renal disease
  - Adverse events
  - Anti-PLA2R levels
  - Quality of life (KDQOL-SF)
  - Proteinuria
  - Creatinine clearance

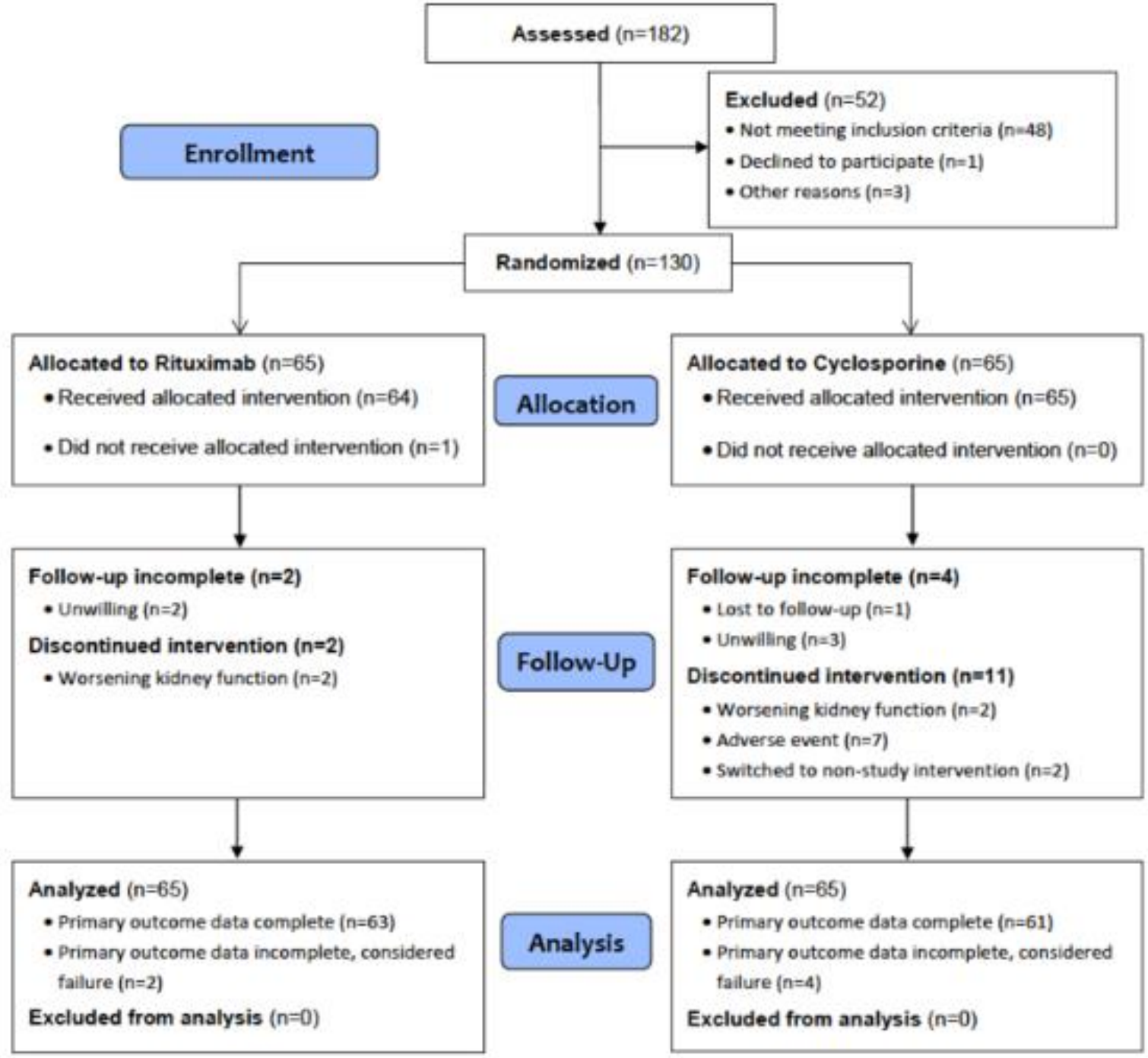

Screening
Conservative Therapy*
Baseline ("Time 0")
Rituximab
Cyclosporine
6 months
6 months
NR
Partial Response
CR
NR
Partial Response
CR
Failure
Retreat at 6 months
Observation (6 months)
Failure
Continue Rx
Observation (6 months)
Exit
6 months
Exit
6 months
Treatment stops at 12 months
Treatment stops at 12 months
Observation for 12 months
Observation for 12 months

Methods – Statistical Analysis

- 63 patients per group required for 80% statistical power
- Non inferiority margin of 15%
- Intention to treat analysis
- If non inferiority significant further analysis to assess superiority of rituximab planned

Results - Patients

- 182 patients screened
- 130 patients enrolled (65 in each arm)


Assessed (n=182)
Enrollment
Excluded (n=52)
• Not meeting inclusion criteria (n=48)
• Declined to participate (n=1)
• Other reasons (n=3)
Randomized (n=130)
Allocated to Rituximab (n=65)
• Received allocated intervention (n=64)
• Did not receive allocated intervention (n=1)
Allocation
Allocated to Cyclosporine (n=65)
• Received allocated intervention (n=65)
• Did not receive allocated intervention (n=0)
Follow-up incomplete (n=2)
• Unwilling (n=2)
Discontinued intervention (n=2)
• Worsening kidney function (n=2)
Follow-Up
Follow-up incomplete (n=4)
• Lost to follow-up (n=1)
• Unwilling (n=3)
Discontinued intervention (n=11)
• Worsening kidney function (n=2)
• Adverse event (n=7)
• Switched to non-study intervention (n=2)
Analyzed (n=65)
• Primary outcome data complete (n=63)
• Primary outcome data incomplete, considered failure (n=2)
Excluded from analysis (n=0)
Analysis
Analyzed (n=65)
• Primary outcome data complete (n=61)
• Primary outcome data incomplete, considered failure (n=4)
Excluded from analysis (n=0)

Results – Clinical Outcomes

- A total of 39 patients (60%) in the rituximab group and 13 (20%) in the cyclosporine group had a primary composite outcome of complete or partial remission at 24 months (risk difference, 40 percentage points; 95% CI, 25 to 55)
- At 24 months, 23 patients (35%) in the rituximab group and none of the patients in the cyclosporine group had a complete remission (risk difference, 35 percentage points; 95% CI, 24 to 47)

Table 2. Composite Outcome of Complete or Partial Remission at 6 to 24 Months.*

Time from Randomization	Rituximab	Cyclosporine	Risk Difference (95% CI)
	no. of patients with remission/total no. (%)		*percentage points*
Intention-to-treat population			
6 mo	23/65 (35)	32/65 (49)	−14 (−31 to 3)
12 mo	39/65 (60)	34/65 (52)	8 (−9 to 25)
18 mo	40/65 (62)	15/65 (23)	38 (23 to 54)
24 mo	39/65 (60)	13/65 (20)	40 (25 to 55)
Per-protocol population			
6 mo	22/63 (35)	32/63 (51)	−16 (−33 to 1)
12 mo	38/63 (60)	33/63 (52)	8 (−9 to 25)
18 mo	39/63 (62)	15/63 (24)	38 (22 to 54)
24 mo	39/63 (62)	13/63 (21)	41 (26 to 57)

* The intention-to-treat population included all the patients who underwent randomization, and the per-protocol population included all the patients who received a full course of trial medications, defined as at least one completed 6-month treatment cycle, according to the protocol. The primary outcome was the composite of complete or partial remission at 24 months. The primary noninferiority analysis and the superiority analysis of the primary outcome at 24 months were performed in the intention-to-treat population, and an additional noninferiority analysis of the primary outcome at 24 months was performed in the per-protocol population. Because the widths of the 95% confidence intervals for secondary outcomes were not adjusted for multiple comparisons, these intervals should not be used for inference about treatment effects.

Evaluation Time Point	Rituximab (N=65)	Cyclosporine (N=65)	Risk Difference (95% CI)	P Value for Noninferiority	P Value for Superiority
	no. with complete or partial remission (%)		*percentage points*		
End of treatment period at 12 mo	39 (60)	34 (52)	8 (–9 to 25)	0.004	—
End of follow-up at 24 mo	39 (60)	13 (20)	40 (25 to 55)	<0.001	<0.001

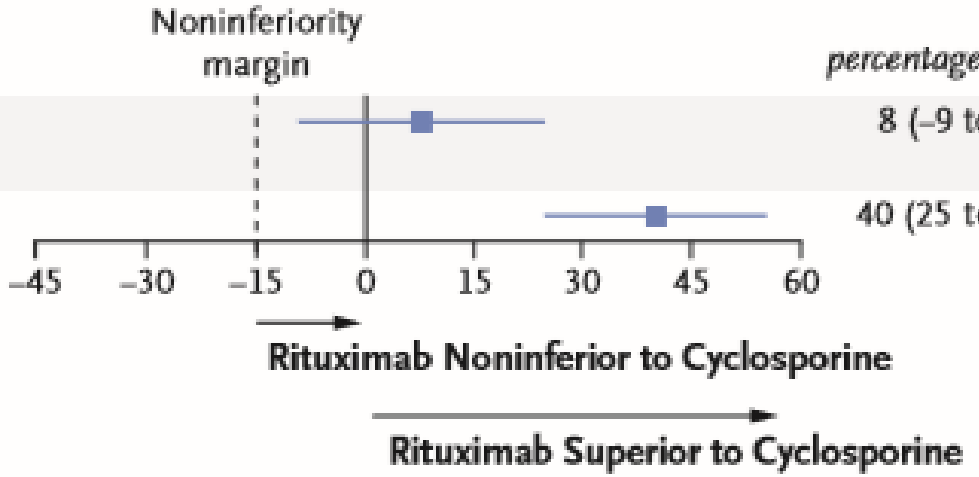


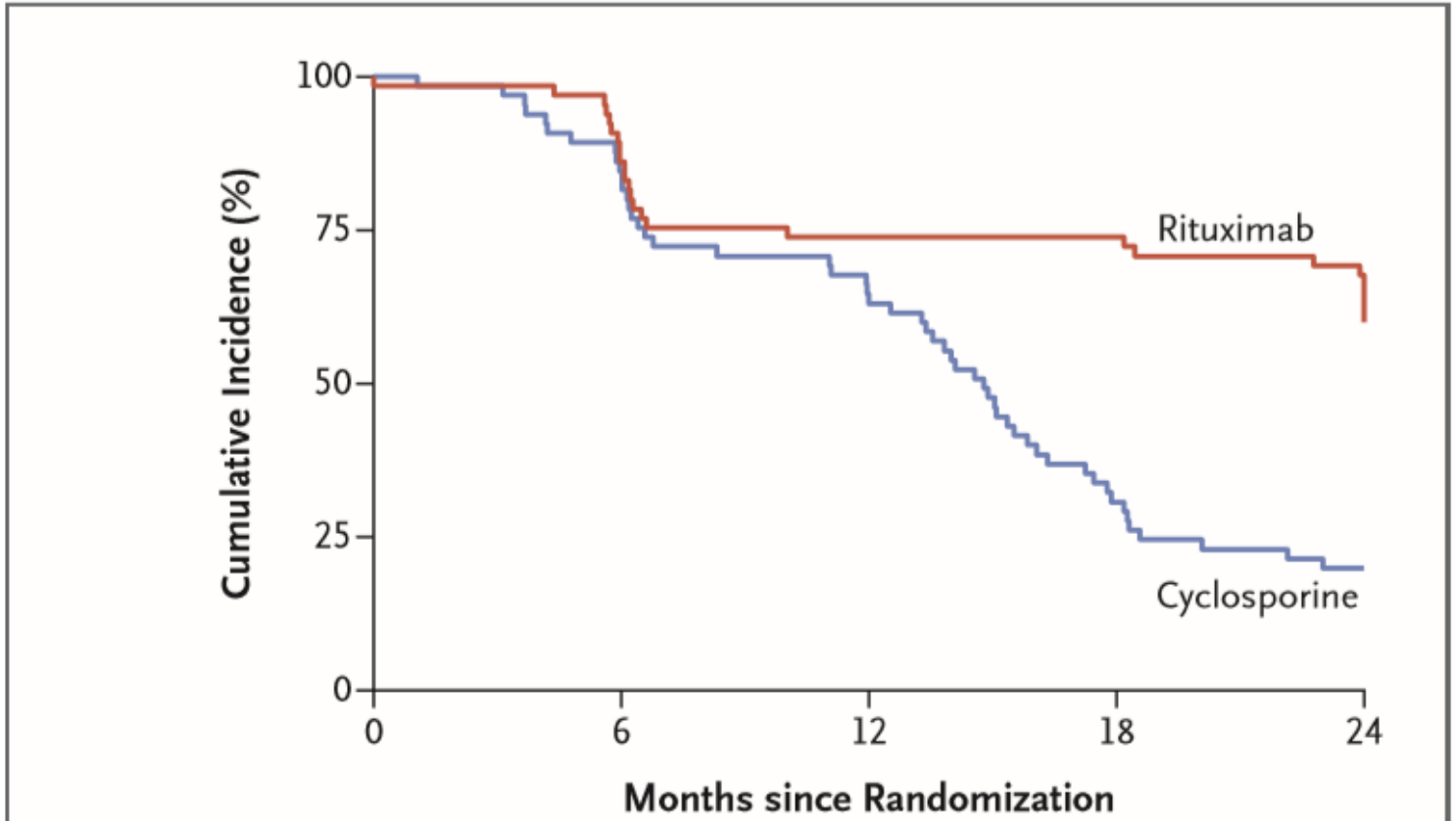
Figure 1. Composite Outcome of Complete or Partial Remission at 12 and 24 Months.

Point estimates and two-sided 95% confidence intervals are shown for the treatment effect, defined as the risk difference for complete or partial remission between groups in the intention-to-treat analysis. The noninferiority margin for rituximab as compared with cyclosporine was –15 percentage points. The lower end of the two-sided 95% confidence interval of the risk difference in the secondary composite of complete remission or partial remission at 12 months was above –15 percentage points, and the P value for noninferiority of 0.004 was significant, which met the prespecified alpha level of a P value of less than 0.0125 after Bonferroni correction. Per the statistical analysis plan, no test for superiority was performed for the secondary outcome of complete or partial remission at 12 months. The lower limit of the two-sided 95% confidence interval for the risk difference in the primary composite outcome of complete remission or partial remission at 24 months was above 0 percentage points; both the criterion for noninferiority and the criterion for superiority of rituximab were met at a P value of less than 0.001, which met the prespecified alpha levels specified for noninferiority ($P<0.025$) and superiority ($P<0.05$). P values for noninferiority are one-sided, and the P value for superiority is two-sided.

Results – Clinical Outcomes

- A total of 26 patients (40%) in the rituximab group and 52 (80%) in the cyclosporine group had treatment failure by 24 months (hazard ratio, 0.34; 95% CI, 0.21 to 0.54)

Results – Clinical Outcomes



No. at Risk

Rituximab	65	59	48	48	44
Cyclosporine	65	56	42	20	13

Figure 2. Time to Treatment Failure.

Results – Laboratory Outcomes

- The decline in anti-PLA2R antibody levels was faster and of greater magnitude and duration in anti-PLA2R–positive patients in remission in the rituximab group than in those in the cyclosporine group and was accompanied by a greater decline in proteinuria.
- The anti-THSD7A–positive patient who had been assigned to the rituximab group was anti-THSD7A–negative from 3 months onward and then had a partial remission at 9 months and a complete remission at 12 months, which was maintained until 24 months.

Results – Adverse Events

- The incidence of adverse events was similar in the rituximab group and the cyclosporine group (71% and 78% of patients, respectively).
- The incidence of adverse events of grade 3 or higher was 52% in the rituximab group and 68% in the cyclosporine group
- The incidence of serious adverse events was 17% and 31%, respectively
- Increased serum creatinine levels and gastrointestinal events were more common with cyclosporine
- Pruritus and infusion-related reactions were more frequent with rituximab.
- End-stage renal disease developed in one patient in the cyclosporine group.

Discussion

- Rituximab non inferior at 12 months and superior at 24 months
- Adverse events similar in the two groups but more serious adverse events with cyclophosphamide
- CD19+ B-cell counts remained low at 12 months therefore residual therapeutic effect of rituximab can’t be ruled out. (no previous published evidence to support this)

Strengths

- RCT
- Adequate statistical power
- 2 year follow up

Weaknesses

- Oral cyclophosphamide used as comparator
  - Authors cite difficulties with compliance.
- Not blinded
- No ethnicity data

Other trials

- STARMEN trial (tacrolimus-rituximab vs methylprednisolone-cyclophosphamide)
- RI-CYCLO (rituximab vs steroids and cyclophosphamide)

References

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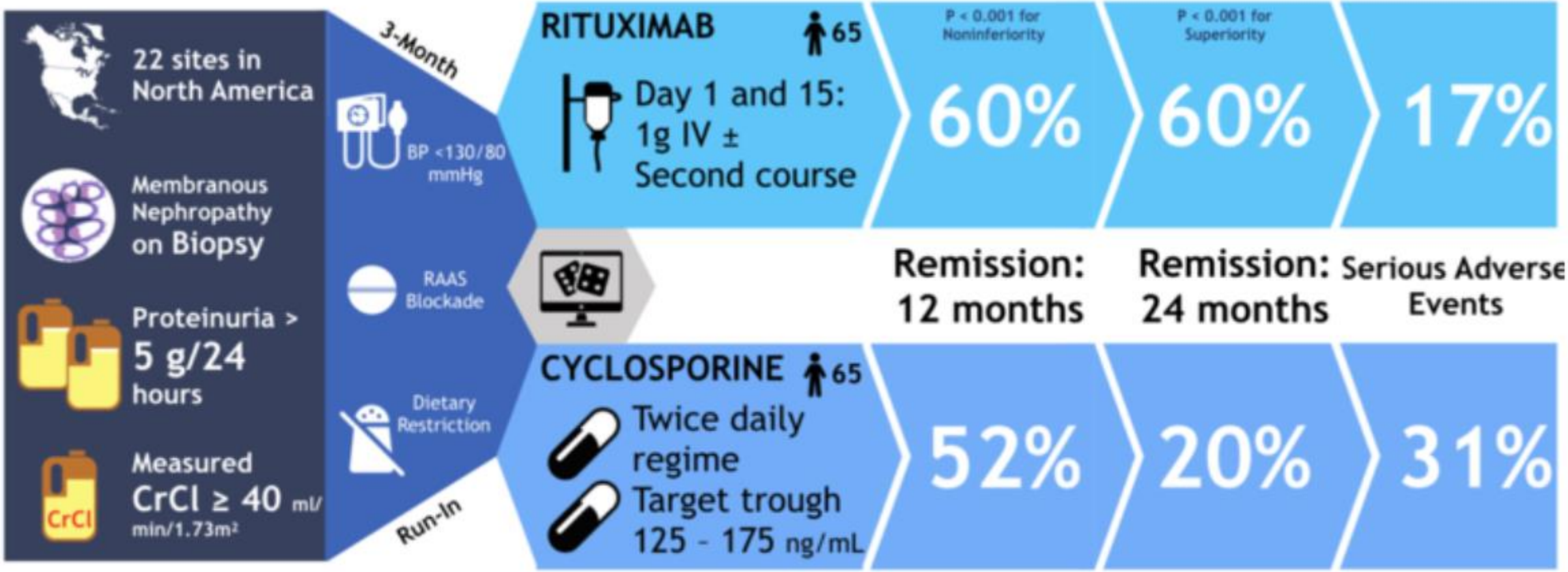
MENTOR: MEmbranous Nephropathy Trial Of Rituximab

#NephJC



Results: in this randomized non-inferiority trial comparing cyclosporine to rituximab in the treatment of membranous nephropathy, rituximab was non-inferior to cyclosporine in inducing complete or partial proteinuria remission at 12 months and was superior in maintaining long-term proteinuria remission up to

Rituximab or Cyclosporine in the Treatment of Membranous Nephropathy. Fervenza FC, Appel GB, Barbour SJ, Rovin BH, Lafayette RA et al. N Engl J Med 2019;381:36-46.

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