University Health Network

Toronto General Hospital Toronto Western Hospital Princess Margaret Hospital

Clinical and Molecular Predictors of Progression: Who Should be Treated?

Heather N. Reich MD PhD FRCPC

University of Toronto

Outline

- Challenges in ascertaining the natural history
- Clinical predictors of outcome
  - Proteinuria: The benchmark biomarker?
  - Unanswered questions regarding histo-pathologic markers
- Molecular markers
  - Conceptual models
  - State of the art

Outline

- **Challenges in ascertaining the natural history**
- Clinical predictors of outcome
  - Proteinuria: The benchmark "biomarker"?
  - Unanswered questions regarding histo-pathologic markers
- Molecular markers
  - Conceptual models
  - State of the art

University Health Network

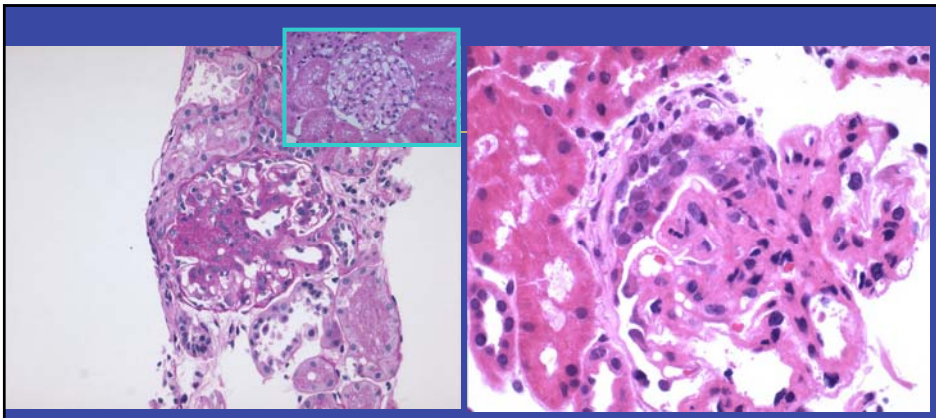
PRELIMINARY SLIDES

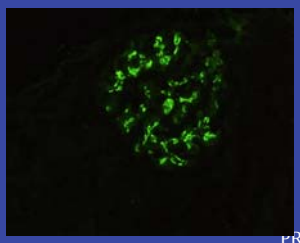
Case presentation

- 29 year old
- Syn-pharyngitic macroscopic hematuria, resolved
  - Blood pressure 90/60
  - Proteinuria 0.8g/24h
  - Serum creatinine 0.6 mg/dL (53 umol/L)

University Health Network

PRELIMINARY SLIDES





IgA

PRELIMINARY SLIDES

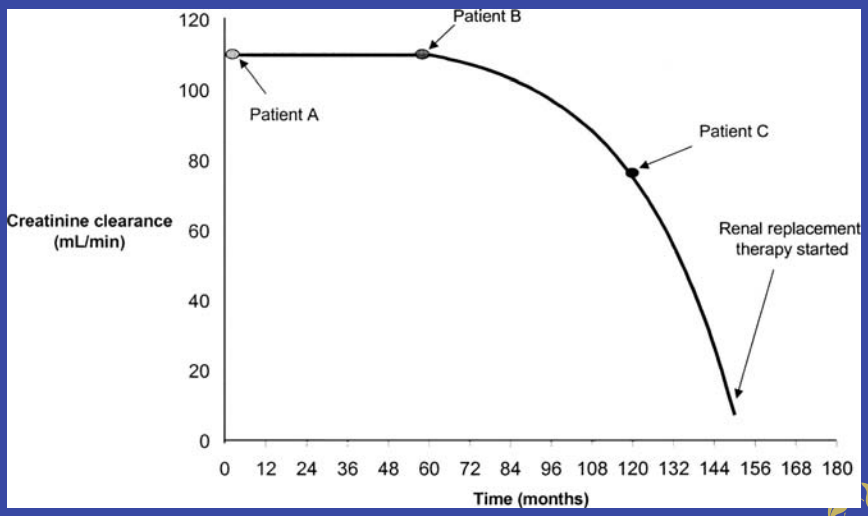
University Health Network

Challenges

- Clinically heterogeneous disease
- Challenges to ascertaining the natural history include:
  - Disease heterogeneity and diagnostic biases
  - Slow progression
  - Measures of therapeutic effects

PRELIMINARY SLIDES

University Health Network



Geddes NDT 2001

PRELIMINARY SLIDES

University Health Network

Table 1. Actuarial Renal Survival at 10 Years, and Clinical Features at Presentation, In Large Populations of Adult Patients With IgAN, According to the Most Accurate Studies of the Literature

Authors and Country	No. of Patients	Mean Age at Presentation (yr)	High Serum Creatinine (%)	High Blood Pressure (%)	Proteinuria >3 g/24 Hours	History of Macroscopic Hematuria (%)	Mean Duration of Follow-up (months)	Actuarial Renal Survival at 10 Years
	Clinical Features at Presentation							
Europe								
D'Amico et al (1986), Italy[5]	365	29	24	36	7%	55	79	85%*
Beukhof et al (1986), The Netherlands[6]	75	24	—	37				84%*
Droz et al (1984)[7]; Noël et al (1987), France[8]	280	—	—	6				85%*
Velo et al (1987), Spain[9]	153	22	—	—				81%*
Bogenschutz et al. (1990), Germany[10]	239	—	34	19				81%†
Rekola et a. (1989, 1990), Sweden[11,12]	209	25	10	11	1%	64	76	89%‡
Alamartine et al. (1991), France[13]	282	28	2	9	3%	27	96	94%*
Johnston et al. (1992), UK[14]	220	30	28	26	32%	—	65	83%‡
Payton et al. (1988), UK[15]	67	32	—	40	—	—	—	77%*
Australia								
Nicholls et al. (1984)[16]	244	32	36	4				87%‡
Ibels et al. (1994)[17]	121	39	36	3				93%*
Asia								
Woo et al. (1986), Singapore[18]	151	27	6	3				91%‡
Kusumoto et al. (1987), Japan[19]	87	27	—	31	15%	—	114	80%*
Katafuchi et al. (1994), Japan[20]	225	32	36	22	16%	20	48	74%‡
Yagame et al. (1996), Japan[21]	206	30	—	—	—	—	110	87%‡
Koyama et al. (1997), Japan[22]	448	>10 in 95%	19	29	3%	24	142	85%*
Li et al. (2002), Hong Kong[23]	168	33	—	28	5%	20	88	82%‡
North America								
Wyatt et al. (1984), USA[24]	58	27						78%*
Radford et al. (1997), USA[25]	148	39	56					67%‡
Haas (1997), USA[26]	109	~40	mean = 2.2 ± 1.9 mg/dL					57%‡
Bartosik et al. (2001), Canada[27]	298	36	—	—	—	—	76	65%*

* From the time of diagnosis.
† Not specified.
‡ From the time of biopsy.

Europe: 84 %

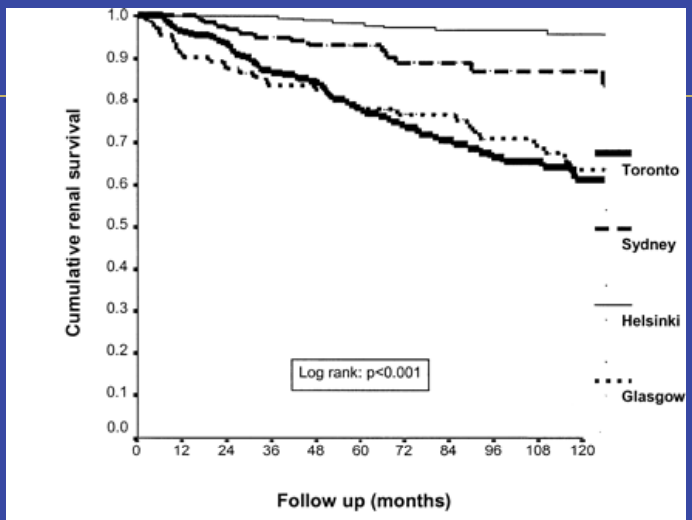
Asia: 83 %

N. America: 66 %

D'Amico Sem Nephrol 2004: 179

PRELIMINARY SLIDES

University Health Network



Number available for study	1yr	3yr	5yr	10yrs
Toronto	258	192	123	41
Sydney	121	111	73	28
Helsinki	204	196	166	109
Glasgow	102	90	78	34

Geddes NDT
2003: 1541

University Health Network

Table 1. Clinical characteristics of patients with biopsy-proven IgA nephropathy at presentation

	Glasgow ($n=112$)	Helsinki ($n=204$)	Sydney ($n=121$)	Toronto ($n=274$)	P
All subjects					
Median year of presentation (range)	1989 (77–95)	1987 (80–95)	1985 (59–93)	1984 (63–97)	–
Median follow up (months)	86	123	73	53	< 0.001[a]
Mean age (years)	37.3	34.9	33.9	37.0	0.05[b]
Male:female ratio	4.6	1.7	1.5	1.8	< 0.001[c]
Median serum creatinine (μmol/l)	118	90	110	115	< 0.001[a]
Mean CrCl (ml/min)	79.1	98.7	82.6	74.2	< 0.001[b]
Median urine protein (UP) excretion (g/day)	1.72	0.64	1.28	1.75	< 0.001[a]
Proportion with UP < 0.5 g/day	22.9%	46.4%	26.2%	5.8%	< 0.001[c]
Mean of mean arterial blood pressure (mmHg)	105	94.0	103	105	< 0.001[b]
Subjects presenting CrCl < 75 ml/min					
Number (%)	52 (46.4)	34 (16.7)	51 (42.1)	132 (48.2)	< 0.001[c]
Mean age (years)	45.3	47.6	37.7	39.1	< 0.001[b]
Mean CrCl (ml/min)	44.1	55.8	52.1	52.2	0.003[b]
Median urine protein (UP) excretion (g/day)	2.24	1.28	1.28	2.2	0.006[a]
Mean of mean arterial blood pressure (mmHg)	107	102	109	108	0.223[b]

[a]Kruskal–Wallis test of variance.
[b]Test of analysis of variance (ANOVA).
[c]4×2 χ^2 test.

University Health Network

Geddes NDT
2003: 1541

PRELIMINARY SLIDES

Outline

- Challenges in ascertaining the natural history
- **Clinical predictors of outcome**
  - **Proteinuria: The benchmark "biomarker"?**
  - **Unanswered questions regarding histo-pathologic markers**
- Molecular markers
  - Conceptual models
  - State of the art

University Health Network

PRELIMINARY SLIDES

Prediction of prognosis

- Clinical variables alone account for 1/3 of the variability in outcome
- Presentation vs. longitudinal measures
- Individuals vs. populations
- Proteinuria: The benchmark biomarker

University Health Network

PRELIMINARY SLIDES

Statistical power

	n	Observed person-years	No. of ESRD	7-year cumulative incidence of ESRD	
				%	95% CI
Sex					
Female	1165	6315.2	76	8.2	6.3–10.0
Male	1104	5608.3	131	15.2	12.7–17.7

- Baseline covariates
- MAP, 24h urine protein excretion, histologic grade

Wakai NDT 2006: 2800

PRELIMINARY SLIDES

University Health Network

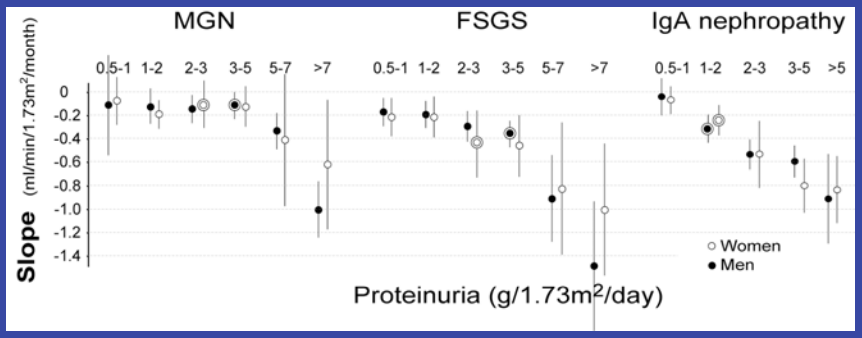
Table 2. Factors at presentation and during follow-up influencing decline in renal function (slope in ml/min per 1.73 m^2/mo) by univariate and multivariate regression[a]

Parameter	Univariate		Multivariate	
	Mean/Standardized β	*P*	Mean/Standardized β	*P*
Presentation				
ln(24 h Upro)[b]	−0.145/−0.258	<0.01	–	NS
MAP	−0.005/−0.145	<0.01	–	NS
Follow-up				
ln(24 h Upro)[b]	−0.258/−0.403	<0.01	−0.302/−0.493	<0.01
MAP	−0.020/−0.337	<0.01	−0.013/−0.231	<0.01
BP med	−0.088/−0.105	0.02	–	NS
ACEi/ARB[c]	0.227/0.092	0.03	0.077/0.124	0.02

Reich JASN 2007: 3177

PRELIMINARY SLIDES

University Health Network



Troyanov NDT 2007:2247

PRELIMINARY SLIDES

University Health Network

Clinical predictors – bottom line

- Longitudinal evaluation of proteinuria overwhelms the analysis of cross sectional prognostic variables – burden is to prove independence and/or additive value
- Prognostic information gleaned from all molecular predictors must be additive to the information provided by proteinuria

PRELIMINARY SLIDES

University Health Network

Histologic information

- Renewed potential for cross-sectional information (clinical, *molecular*) to predict prognosis

University Health Network

PRELIMINARY SLIDES

Table 5| Correlations between pathological features and outcomes: univariate and multivariate pathologic determinants of slope

	Rate of renal function decline (linear regression)			Survival from renal failure or a 50% drop in GFR (Cox regression)		
	Univariate slope (ml/min per 1.73 m^2 per year)	Multivariate[a]		Univariate hazard ratio (95% CI)	Multivariate[a]	
		Model A β (s.d.)	Model B β (s.d.)		Model A	Model B
Mesangial hypercellularity score						
≤0.5	−0.5 ± 3.3	−2.2 (1.3)	−0.8 (1.2)	0.06 (0.01-0.45)	0.07 (0.01-0.53)	0.11 (0.01-0.80)
>0.5	−4.2 ± 9.0			1	1	1
	P<0.001	*P*=0.10	*P*>0.1	*P*=0.006	*P*=0.01	*P*=0.03
Segmental glomerulosclerosis						
Absent	−0.5 ± 7.5			1	1	1
Present	−4.4 ± 8.4	−3.6 (1.3)	−2.5 (1.1)	3.1 (1.4-7.3)	1.8 (0.5-5.3)	2.5 (0.9-7.3)
	P=0.001	*P*=0.005	*P*=0.03	*P*=0.009	*P*>0.1	*P*=0.09
Tubular atrophy/interstitial fibrosis[b]						
0–25%	−2.5 ± 7.6	−5.2 (1.1)	−3.7 (1.0)	1	1	1
26–50%	−5.7 ± 8.8			3.5 (1.9-6.5)	5.0 (2.7-13.9)	5.0 (2.3-11.1)
>50%	−11.1 ± 12.6			15.5 (7.5-31.5)	17.3 (5.9-50.9)	8.8 (2.9-26.4)
	P<0.001	*P*<0.001	*P*<0.001	*P*<0.001	*P*<0.001	*P*<0.001

CI, confidence interval; GFR, glomerular filtration rate; MAP, mean arterial pressure.
Endocapillary, extracapillary, and arterial lesions were not associated with the rate of renal function decline or survival from renal failure or a 50% drop in GFR (see text. Correlations between pathological lesions and outcome).
[a]Model A: multivariate with three pathological features + initial GFR, MAP, proteinuria. Model B: multivariate with three pathological features + initial GFR and follow up MAP and proteinuria.
[b]Outcomes with 0% tubular atrophy/interstitial fibrosis were identical to 1–25% tubular atrophy/interstitial fibrosis hence the two categories were combined to maximize statistical power.

The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification

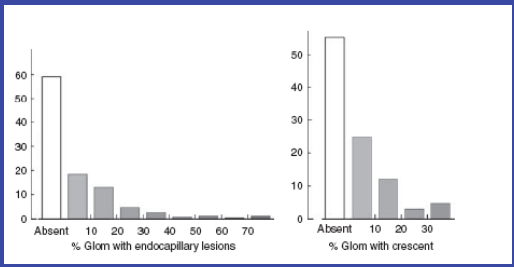
University Health Network

PRELIMINARY SLIDES

KI 2009: 534, 546

Unanswered questions: Histopathology

- Endo and extracapillary proliferation
  - Numbers
  - Important interaction with therapy



KI 2009: 534, 546

PRELIMINARY SLIDES

University Health Network

Outline

- Challenges in ascertaining the natural history
- Clinical predictors of outcome
  - Proteinuria: The benchmark "biomarker"?
  - Unanswered questions regarding histo-pathologic markers
- **Molecular markers**
  - **Conceptual models**
  - **State of the art**

PRELIMINARY SLIDES

University Health Network

Conceptual models

- Cross sectional vs. longitudinal
  - Realistic to use info from a single point in time?
  - Response to therapy important
  - New surrogate markers
- Candidate driven vs. hypothesis generating approaches

University Health Network

PRELIMINARY SLIDES

State of the art

- Tissue
  - Phenotypic heterogeneity = molecular heterogeneity
  - Translational models
- Urine / Serum
  - IgA-specific
    - Ex. glycan-specific IgG antibodies
  - Non-specific activity / fibrosis
    - Ex. EGF / MCP-1

University Health Network

PRELIMINARY SLIDES