

The Euro-Lupus regime as treatment for lupus nephritis

Renal Week 2010
Denver

Frédéric A. Houssiau



Rheumatology Unit
Internal Medicine Department
Cliniques Universitaires Saint-Luc, Brussels
Université catholique de Louvain, Belgium



Frédéric A. Houssiau Disclosures

- FAH has received consultant fees from
Aspreva Pharmaceuticals
Bristol Myers Squibb
Human Genome Science
Merck Serrono
UCB
- The Euro-Lupus Nephritis Trial and the MAINTAIN Nephritis trial are non-sponsored investigator-initiated studies

The Euro-Lupus/MAINTAIN Triallists

D. Abramowicz, R. Cattaneo, R. Cervera, J.-P. Cosyns, M.-G. Danieli, D. D'Cruz, G. Depresseux, E. de Ramon, H. Direskeneli, J. Font †, M. Galeazzi, A. Gul, M. Jadoul, J. Jamart, Y. Levy, A. Matthieu, P. Petera, R. Petrovic, R. Popovic, G.-D. Sebastiani, R. A. Sinico, C. Vasconcelos

D. Blockmans, R. Cervera, D. D'Cruz, G. Depresseux, E. De Ramon, C. Fiehn, I.M. Gilboe, L. Guillemin, F.A. Houssiau, V. Le Guern, R. Petrovic, I. Ravelingien, P. Remy, S. Sangle, M. Tektonidou, C. Vasconcelos and the MAINTAIN Nephritis Trial group

EUROPEAN WORKING PARTY ON SLE



French favourite actress enters your office a Friday night

Creat: 1.5 mg/dl
Albumin: 2.2 g/dl
Proteinuria: 6 g/d
C3: 43 mg/dl
C4: <5 mg/dl
Anti-DNA: 2,589 U/ml

What treatment would you advice her ?

This is a fiction for teaching purposes

The NIH IV cyclophosphamide regimen: for so long the standard of care

0.75 - 1 g/m²

WBC nadir (d14): 1,500 - 4,000/ μ l

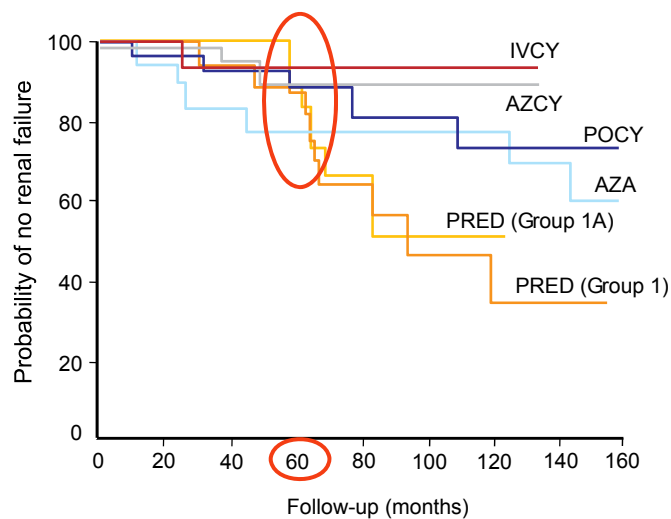
monthly for 6 months

quarterly for 1 year after CR

Mesna (oral or IV; 20 % of total CYC dose at 0, 2, 4 and 6 hours after CYC dosing)

Antiemetics

LN - The need for long-term follow-up



Austin HA et al. *NEJM* 1986; 314: 614.

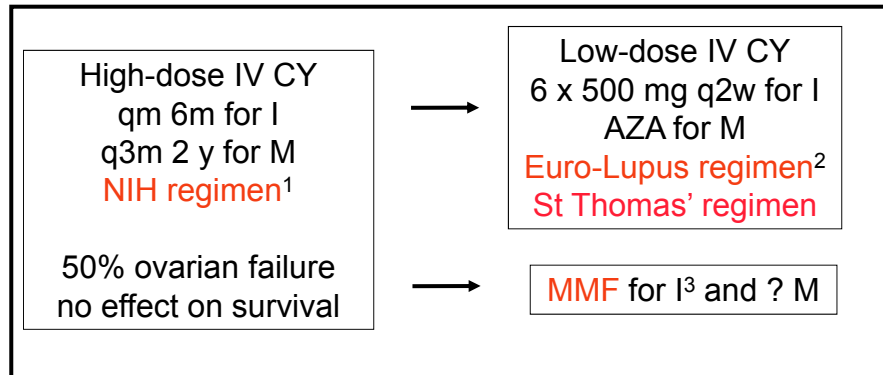
Side-effects of high-dose IVCY

Side-effect	NIH Trials (% patients)		
	<u>1st</u>	<u>2nd</u>	<u>3rd</u>
Infection	10	5	26
H. zoster	25	5	15
Ovarian failure	45	38	52

“With regard to the IVCY treatment itself, a few generations from now a better therapy for lupus nephritis will be available, and the “NIH protocol”, having gone the way of the dinosaurs, will have been forgotten”

Can we get replace of the NIH regimen ?

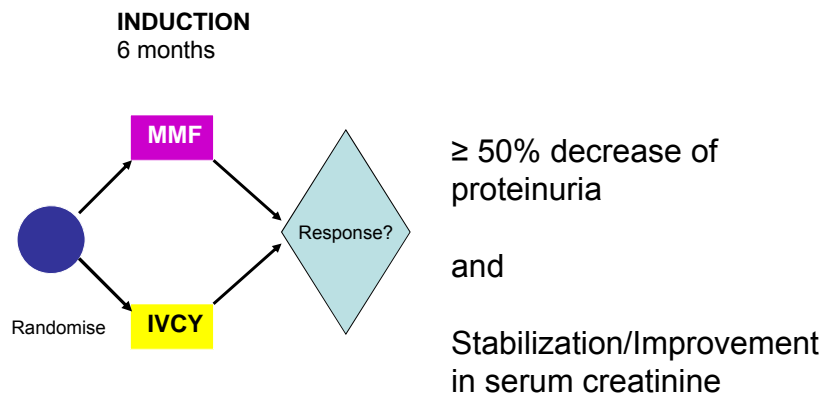
A two-hit saga



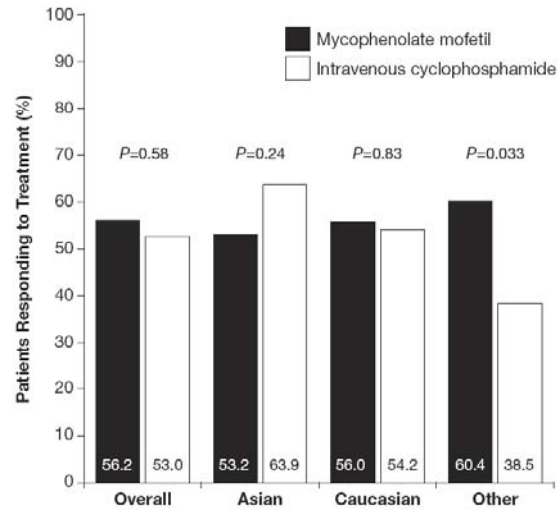
I: Induction
M: Maintenance

¹: Austin NEJM 1986; Boumpas Lancet 1992; Gourley Ann Int Med 1996
²: Houssiau A&R 2002; Houssiau A&R 2004; Houssiau Ann Rheum Dis 2010
³: Ginzler NEJM 2005; Appel JASN 2009

Aspreva Lupus Management Study



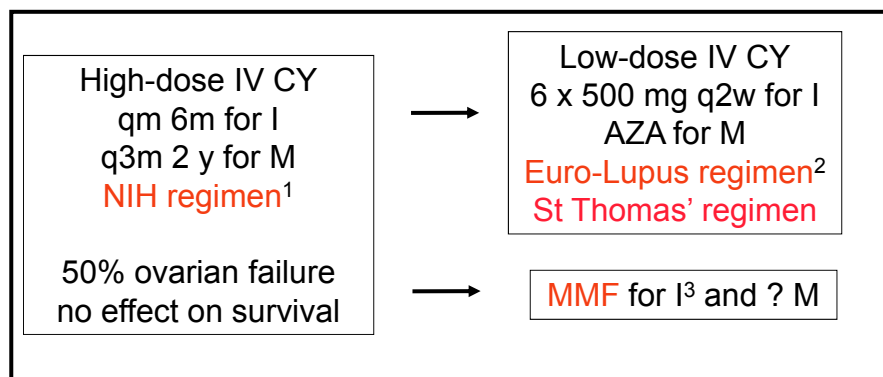
Aspreva Lupus Management Study



Appel GB et al. *J Am Soc Nephrol* 2009, 20: 1103

Can we get replace of the NIH regimen ?

A two-hit saga



I: Induction
M: Maintenance

¹: Austin NEJM 1986; Boumpas Lancet 1992; Gourley Ann Int Med 1996
²: Houssiau A&R 2002; Houssiau A&R 2004; Houssiau Ann Rheum Dis 2010
³: Ginzler NEJM 2005; Appel JASN 2009

Euro-Lupus Nephritis Trial Rationale in 1992

- European patients may differ from American patients
 - Ethnicity (!)
 - Access to therapy (?)
 - Less severe disease (?)

Euro-Lupus Nephritis Trial Sequential therapy concept

- Induction phase
 - incisive treatment
 - possibly toxic
 - short period of time
- Response
- Maintenance phase
 - safe drug
 - long period of time

Low-dose
IVCY

AZA

Euro-Lupus Nephritis Trial

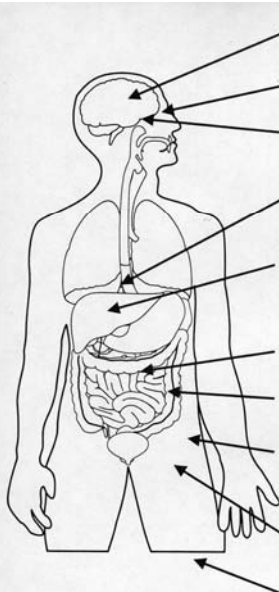
Inclusion criteria

- SLE
- ≥ 14 years of age
- ≥ 500 mg 24h proteinuria
- WHO III, IV, Vc or Vd

Euro-Lupus Nephritis Trial

GC regimen

- 3 daily 750 mg IV MP pulses
- oral pred: 0.5 mg/kg/day
- tapered after 1 month by 2.5 mg q2w
- down to 5-7.5 mg/day at M6



The many targets of glucocorticoids

Steroids

Why we hate them

Why we love them

Brain/CNS:
Depression
Psychosis

Eye:
Glaucoma

Endocrine system:
↓ LH, FSH release
↓ TSH release
↓ GH secretion

GI tract:
Peptic ulcerations

Carbohydrate/lipid metabolism:
↑ hepatic glycogen deposition
↑ peripheral insulin resistance
↑ gluconeogenesis
↑ free fatty acid production
Overall diabetogenic effect

Adipose tissue distribution:
Promotes visceral obesity

Cardiovascular/Renal:
Salt and water retention
Hypertension


Skin/muscle/connective tissue:
Protein catabolism/collagen breakdown
Skin thinning
Muscular atrophy

Bone and calcium metabolism:
↓ bone formation
↓ bone mass and osteoporosis

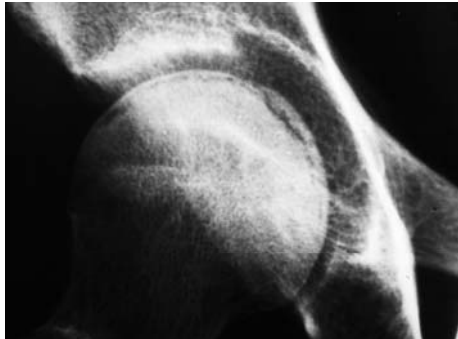
Growth and Development:
↓ linear growth

Immune system:
Anti-inflammatory action
Immunosuppression

Glucocorticoid-induced damage



Vertebral crush



Hip osteonecrosis

Glucocorticoids in SLE

« When you decide a dose of steroids, divide it by two:
it still works! »

Frédéric A Houssiau

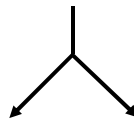
Euro-Lupus Nephritis Trial

STEROIDS

3 x 750 mg IV MP; 0.5 mg/kg/d pred 1 month; tapering

HD IV CY

8 pulses
(0.5 g/m²; up to 1.5 g)
q1 month for 6 m
q3 months for 6 m
start AZA w 44



LD IV CY

6 pulses
500 mg
q2 weeks
start AZA w 12

Euro-Lupus Nephritis Trial Maintenance therapy

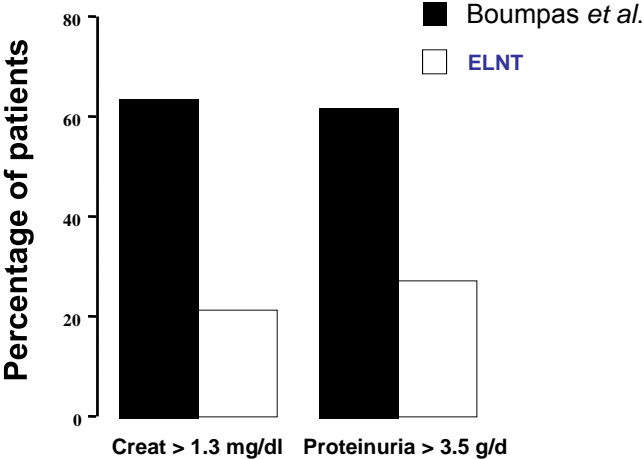
- Up to M30:
 - low-dose pred (5-7.5 mg/day)
 - azathioprine (2 mg/kg/day)
 - detailed protocol reporting

- \geq M30:
 - physician/patient's decision
 - major outcome reporting

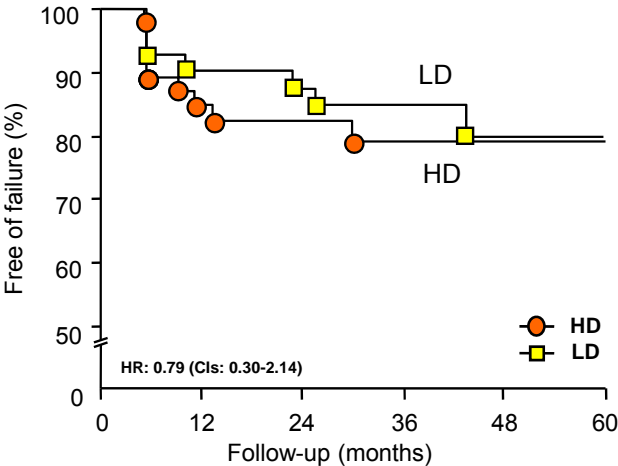
ELNT - Baseline data

Parameter	All (n = 90)	HD IV CY (n = 46)	LD IV CY (n = 44)
Age (years)	31 \pm 11	30 \pm 11	33 \pm 12
Females/Males (n)	84/6	43/3	41/3
Ethnicity			
Caucasian (n)	76	37	39
Asian (n)	6	4	2
Afro-Car./Black (n)	8	5	3
Past history			
Past renal disease (n)	21	11	10
Past GC treatment (n)	55	27	28
Past IS treatment (n)	7	4	3

ELNT - Patients

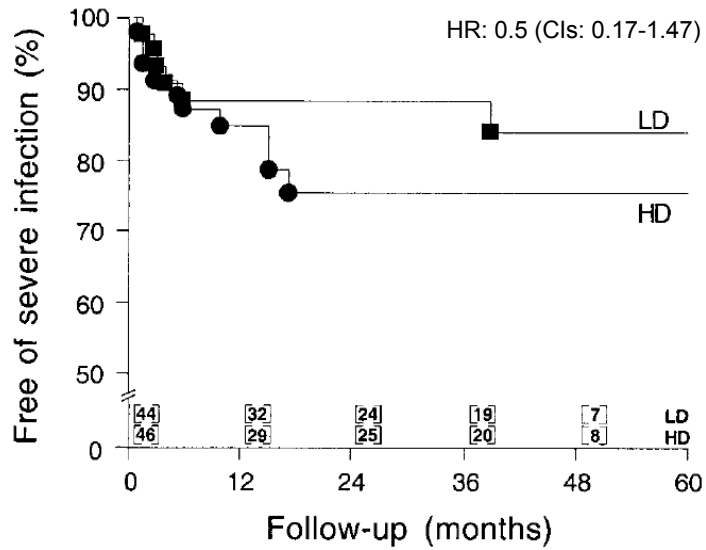


ELNT - Treatment failure



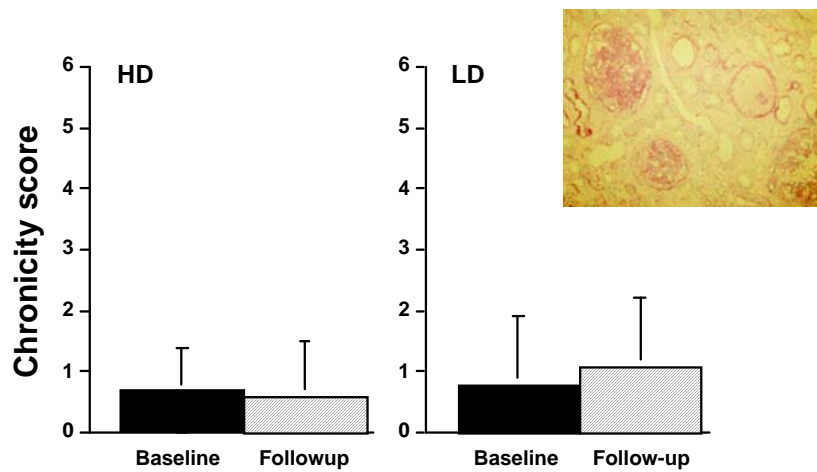
Houssiau FA et al. *Arthritis Rheum* 2002; 46: 2121-2131.

ELNT - Severe Infection



Houssiau FA et al. *Arthritis Rheum* 2002; 46: 2121-2131.

ELNT - Second renal biopsy



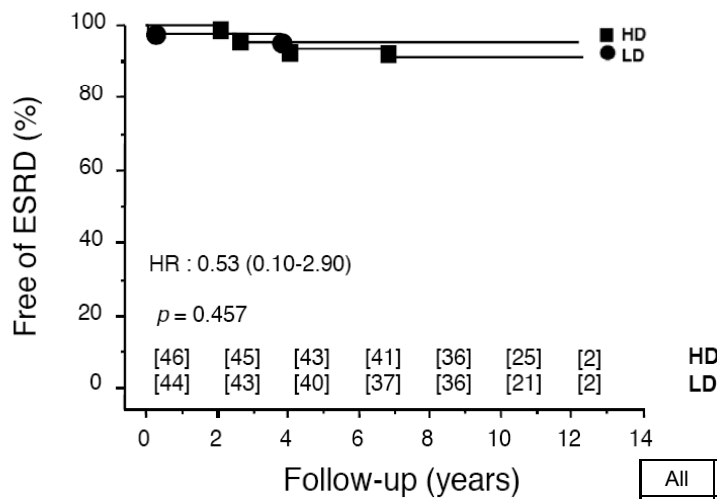
Houssiau FA et al. *Arthritis Rheum* 2004; 50: 3934-3940

ELNT - 10 year FU

	ALL	HD	LD
Randomized (n)	90	46	44
Lost (n)	6	3	3
FU duration (m)	115 ± 30	119 ± 27	111 ± 33
Age (y)	41 ± 12	40 ± 11	42 ± 11

Houssiau FA et al. *Ann Rheum Dis* 2010; 69: 61

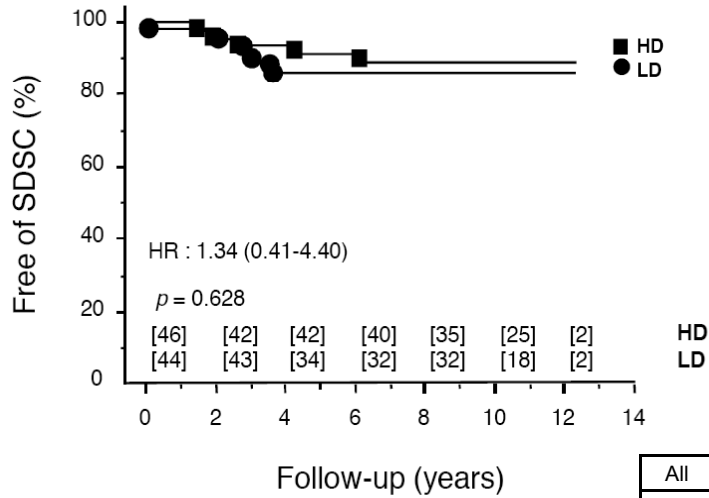
ELNT - 10 year FU - ESRD



Houssiau FA et al. *Ann Rheum Dis* 2010; 69: 61

All	HD	LD
6	4	2
7%	9%	5%

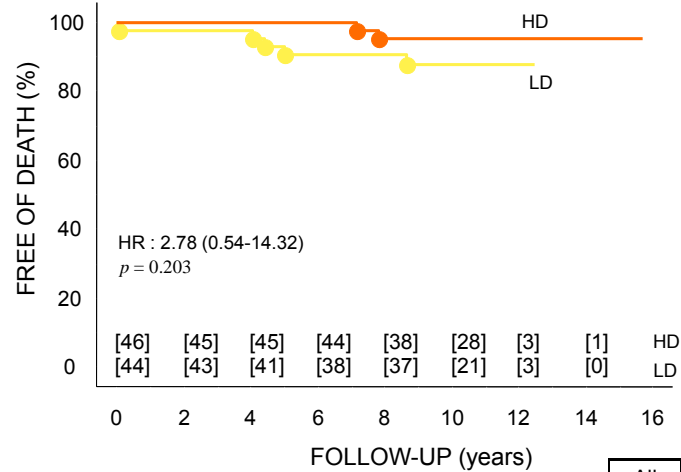
ELNT - 10 year FU - SDSC



Houssiau FA et al. *Ann Rheum Dis* 2010; 69: 61

All	HD	LD
11	5	6
12%	11%	14%

ELNT - 10 year FU - Deaths



Houssiau FA et al. *Ann Rheum Dis* 2010; 69: 61

All	HD	LD
7	2	5
8%	4%	11%

Is the Euro-Lupus regimen efficacious in non-Caucasians ?

LD IV CY arm of the EuroLupus Nephritis Trial:
only 5 non-caucasians...

	Caucasians	Non-Caucasians
Death	4/39	1/5
SDSC	6/39	0/5
ESRD	2/39	0/5

ELNT - 10 year FU

- Euro-Lupus Regime achieves good clinical results in the very longterm
- Death and ESRD rates are low
 - mainly Caucasians
 - moderately severe LN
 - longterm IS (GC and other IS)
 - anti-proteinuric therapy
 - referral centers

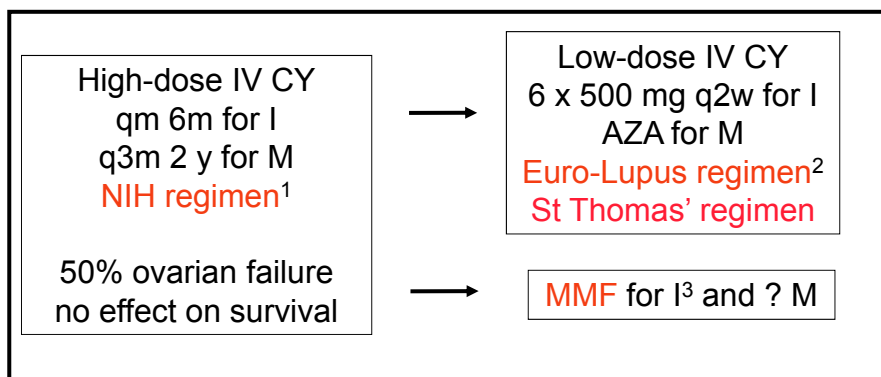
ELNT - 10 year FU

	All	High-dose IVCY	Low-dose IVCY
Current serum creatinine (mg/dl)	1.0 ± 0.5	1.0 ± 0.4	1.0 ± 0.6
Current 24h-proteinuria (g)	0.6 ± 1.2	0.6 ± 1.3	0.5 ± 1.0
Ongoing GC therapy (% of patients)	73	71	75
Ongoing IS therapy (% of patients)	56	59	53
Ongoing BP lowering therapy (% of patients)	68	68	67
Additional IS drugs ever received ^{**} (n)	0.7 ± 0.9	0.7 ± 0.9	0.7 ± 0.9
Ever received MMF (% of patients)	30	30	29
Cumulative IVCY dose (g)	7.6 ± 2.5	9.5 ± 2.5	5.5 ± 4.8 ^{***}

Houssiau FA *et al. Ann Rheum Dis* 2010; 69: 61

Can we get replace of the NIH regimen ?

A two-hit saga



I: Induction

M: Maintenance

¹: Austin NEJM 1986; Boumpas Lancet 1992; Gourley Ann Int Med 1996

²: Houssiau A&R 2002; Houssiau A&R 2004; Houssiau Ann Rheum Dis 2010

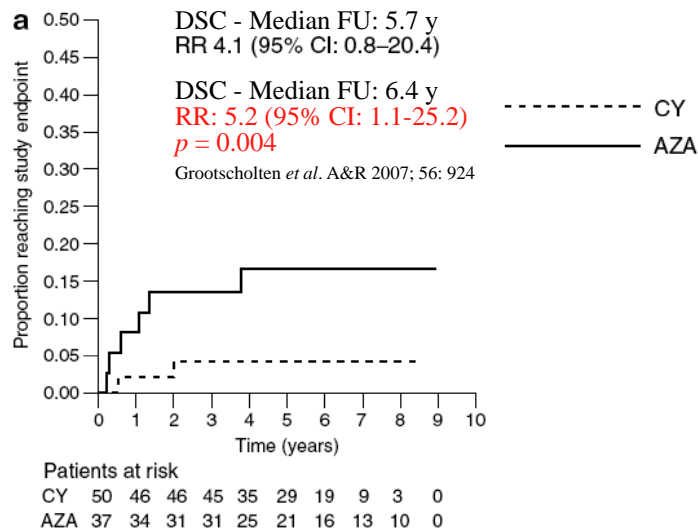
³: Ginzler NEJM 2005; Appel JASN 2009

IV CY or MMF for induction ?

Variables	Induction therapy	
	MMF	IVCY
Non-C/Non-A race	✓	
Future pregnancy wish	✓	
Doubts on compliance		✓
Availability worldwide/Costs		✓

But, before MMF wins the challenge over low-dose IV CY,
we need long-term data!

Dutch LN Study: AZA/MP vs NIH IVCY



Which drug for induction ?

Not all patients will respond to the same drug

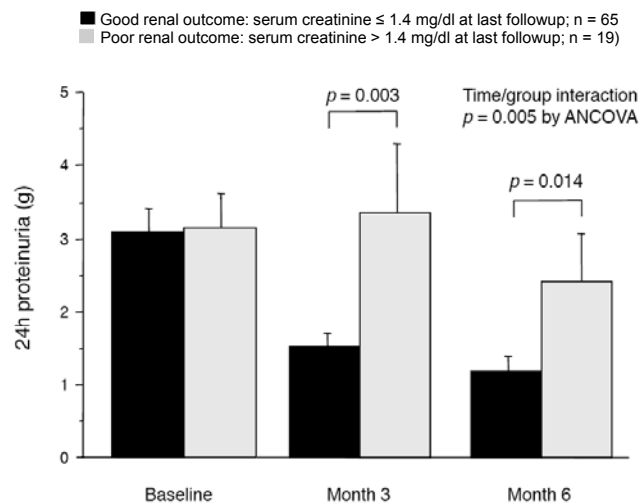
We are very bad in predicting responses to therapy

We mostly use a trial and error approach

In case of non-response, treatment switch is advised

ELNT - 10 year FU

Early response is a good prognostic factor

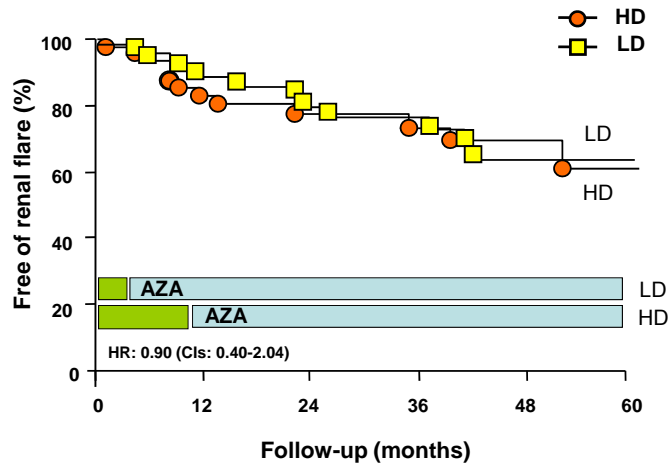


ELNT - early response is predictive for normal longterm renal function

Variable	P	OR	95% CL
Age (< 30 years)	0.99	1.0	0.2-5.1
Gender (female)	0.98	0	NA
Baseline diastolic pressure (<90mmHg)	0.77	1.3	0.3-5.9
Baseline serum creatinine (<1.4mg/dL)	0.06	7.7	0.9-65.6
Baseline serum albumin (<3g/dL)	0.31	0.4	0.1-2.2
Baseline 24hr proteinuria (<3g)	0.81	0.8	0.1-4.6
WHO class (III or Vc)	0.32	0.3	0-3.4
Activity index (<10)	0.53	2.0	0.2-18.4
Chronicity index (<1)	0.11	4.0	0.7-21.9
Treatment allocation (HDIV CYC)	0.33	0.4	0.1-2.3
ACEI use (yes)	0.34	2.3	0.4-12.5
Serum creatinine at 6 months (drop)	0.01	14.9	2.0-1118
24hr proteinuria at 6 months (<1g)	0.03	6.3	1.2-344

Houssiau FA et al. *Arthritis Rheum* 2004; 50: 3934-3940

The Euro-Lupus regime does not efficiently prevent renal relapses



Houssiau FA et al. *Arthritis Rheum* 2002; 46: 2121-2131

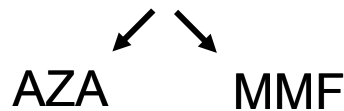
MAINTAIN Nephritis trial

All patients from D1 to W12

Glucocorticoids
IV CYC mini-pulses : 6 x 500 mg q2 weeks

From W12

(whatever the response; randomization performed at baseline)



Houssiau *et al.* Ann Rheum Dis 2010; free access on line

MAINTAIN Nephritis trial

GC + IV CY + AZA

versus

GC + IV CY + MMF

Houssiau *et al.* Ann Rheum Dis 2010; free access on line

The MAINTAIN Nephritis Trial Baseline data

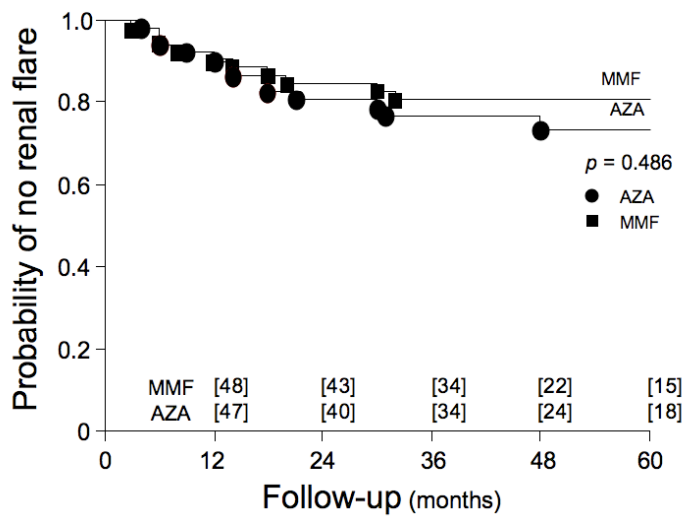
	AZA* (52)	MMF* (53)	<i>P</i>
Serum creatinine (mg/dl)	1.02	1.01	0.834
24-h proteinuria (g)	2.94	3.63	0.190
Serum albumin	3.01	2.97	0.788
Hb (g/dl)	10.96	10.93	0.931
Serum C3 (mg/dl)	55	49	0.873
ECLAM	6.95	6.41	0.873
SLEDAI	17	19	0.156

*: values are means

Houssiau *et al.* Ann Rheum Dis 2010; free access on line

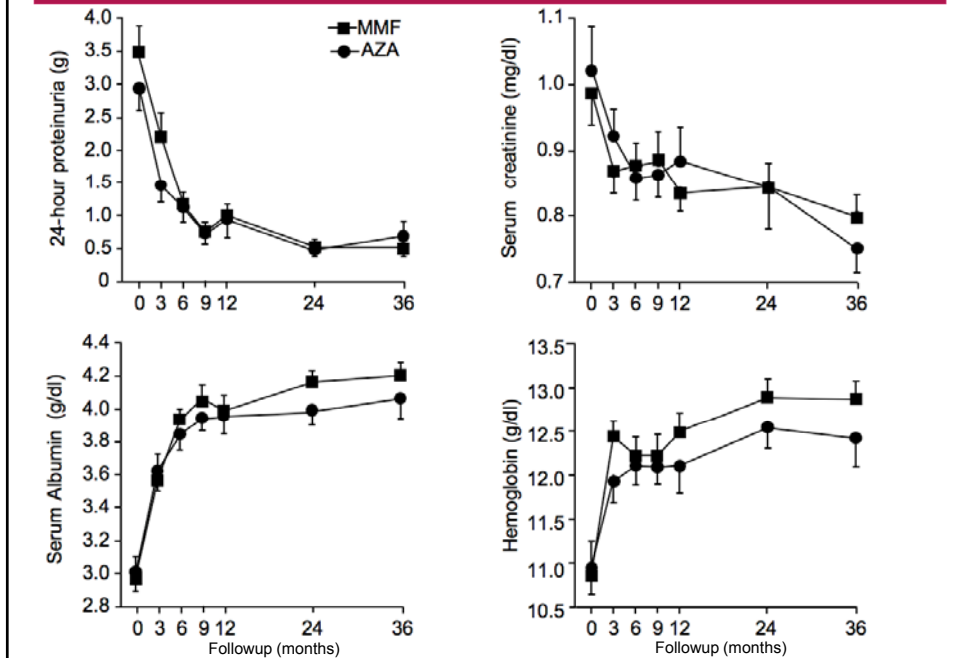
The MAINTAIN Nephritis Trial Primary endpoint: Time to renal flare

Analysis by intention-to-treat



Houssiau *et al.* Ann Rheum Dis 2010; free access on line

The MAINTAIN Nephritis Trial



The MAINTAIN Nephritis Trial - Adverse events

	ALL	AZA	MMF
Benign infection	36	14	22
Gastrointestinal	16	8	8
Hematological	16	14	2
Severe infection	14	6	8
Herpes zoster	12	5	7
Neurological	11	7	4
Metabolic	8	5	3
Skin rash	4	2	2
Amenorrhea	3	1	2
Liver	3	2	1
Alopecia	3	1	2
Haemorrhage	4	2	2
Cervix carcinoma	2	2	0
Cardiovascular	2	2	0
Thromboembolic	2	2	0
Ocular	1	1	0
TOTAL	134	74	60

Houssiau *et al.* Ann Rheum Dis 2010; free access on line

Repeat kidney biopsies fail to detect differences between azathioprine and mycophenolate mofetil maintenance therapy for lupus nephritis: data from the MAINTAIN Nephritis Trial.

M. Stoeniu, S. Aydin, C. Vasconcelos, M. Tektonidou, I. Ravelingien, V. le Guern, G. Depresseux, R. Cervera, F. A. Houssiau and J.-P. Cosyns

on behalf of the MAINTAIN Nephritis Trial Group



Coordinator center
Rheumatology Department
Cliniques Universitaires Saint-Luc
Université catholique de Louvain
Belgium



The MAINTAIN Nephritis Trial
Patients' characteristics

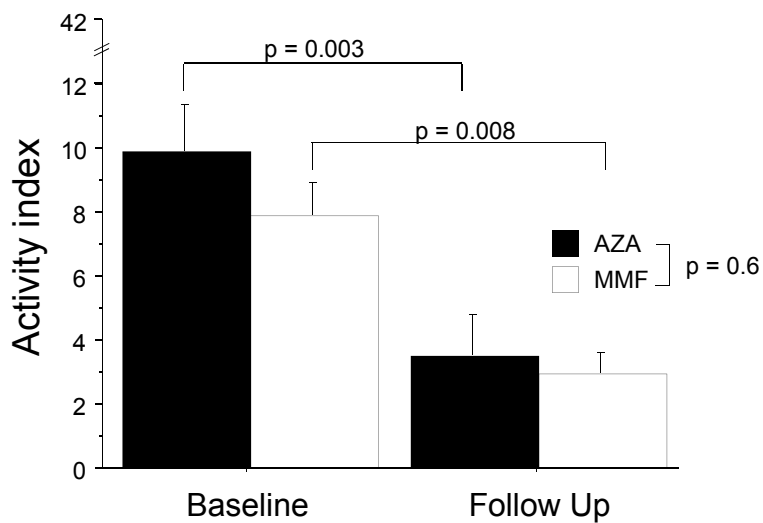
	All	Repeat kidney biopsy
Number of patients	105	30
AZA/MMF	52/53	16/14
Serum creatinine (mg/dl)	1.0 ± 0.4	0.9 ± 0.4
24 h proteinuria (g/24h)	3.2 ± 2.6	3.4 ± 2.8
Serum albumine (mg/dl)	3.0 ± 0.7	2.9 ± 0.8

Per protocol repeat kidney biopsy at 24 ± 6 months

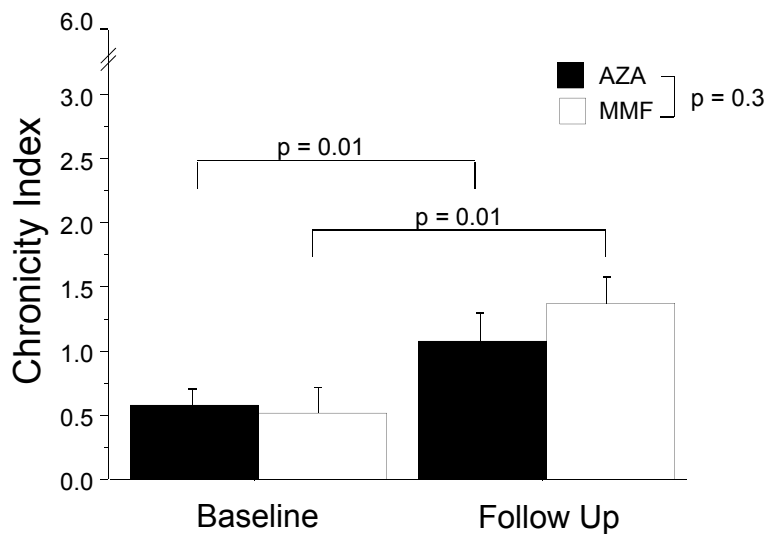
The MAINTAIN Nephritis Trial Patients' characteristics

Repeat kidney biopsies		AZA (16)	MMF (14)
Creatinine (mg/dl)	Baseline	0.8 ± 0.2	1.1 ± 0.5
	Follow-up	0.8 ± 0.2	0.8 ± 0.3
Albumine (g/dl)	Baseline	2.9 ± 0.7	3.0 ± 0.8
	Follow-up	4.1 ± 0.6	4.1 ± 3.2
24h Proteinuria (g/24h)	Baseline	3.3 ± 2.8	3.5 ± 3.0
	Follow-up	0.5 ± 1.1	0.6 ± 1.1

MAINTAIN - Renal pathology - Activity index



MAINTAIN - Renal pathology - Chronicity index

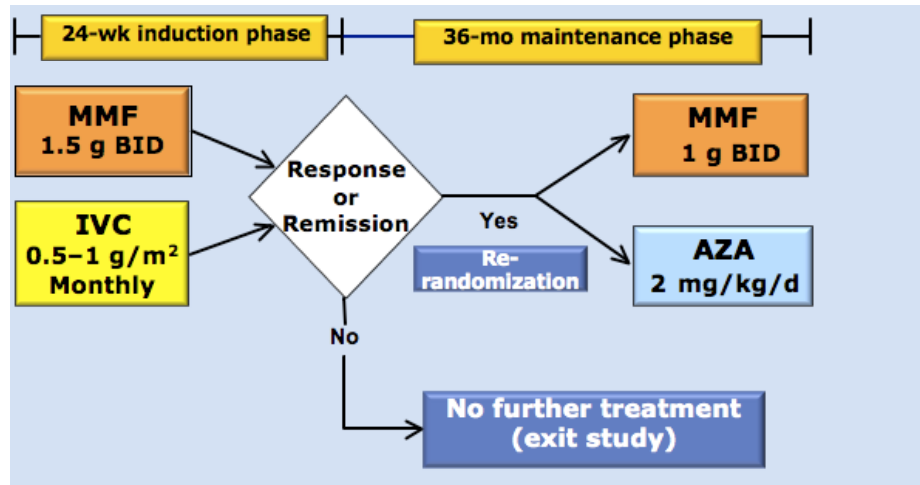


MAINTAIN – Conclusion

Although there was a trend towards a lower renal relapse rate with MMF (19% vs 25%), the difference was not statistically significant

Control renal biopsies, performed in a representative subset of patients, fail to reveal an advantage of one drug over the other

Aspreva Lupus Management Study



Courtesy of David Wofsy

Aspreva Lupus Management Study

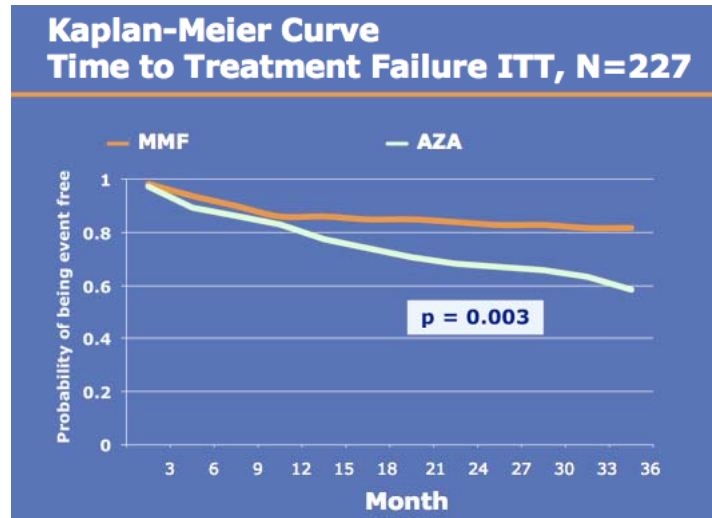
Primary Efficacy Endpoint

Primary endpoint: time to treatment failure
(adjudicated by Clinical Endpoints Committee)

- **Treatment failure, defined as:**
 - Renal flare (proteinuric or nephritic)
 - Sustained doubling of serum creatinine
 - Initiation of rescue therapy for LN
 - End-stage renal disease (ESRD)
 - Death

Courtesy of David Wofsy

Aspreva Lupus Management Study



Courtesy of David Wofsy

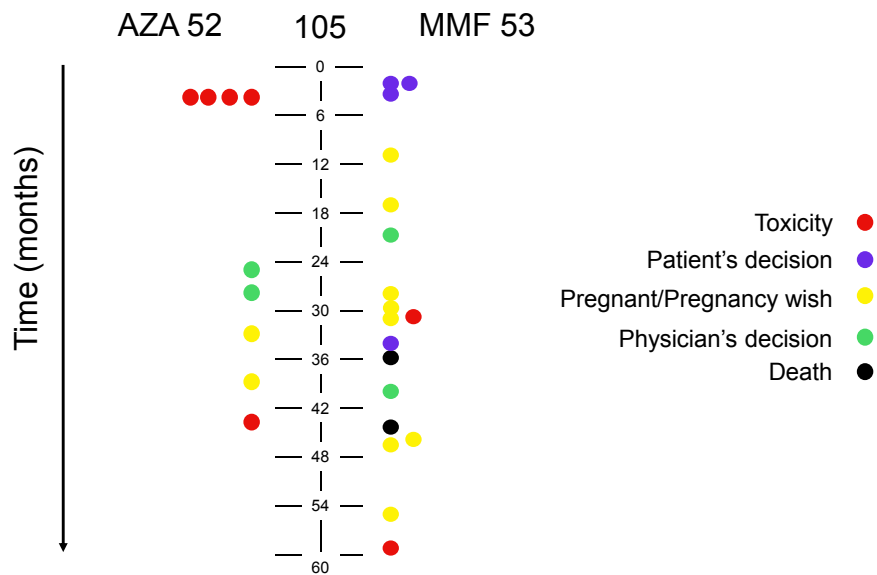
MAINTAIN *versus* ALMS

- Different ethnic background
- ALMS larger study
- Composite endpoint in ALMS
- Only patients with a
« response » were entered in
the ALMS maintenance phase

Maintenance immunosuppression in LN

- At least two drugs are available: AZA and MMF, with \pm similar efficacy/toxicity
- Treatment failures can be rescued ?

The MAINTAIN Nephritis Trial - Drops



Houssiau *et al.* Ann Rheum Dis 2010; free access on line

This makes the difference!



- Patient education
- Obsessional follow up
- Stringent blood pressure control ($\leq 120/80$ mm Hg)
- ACEI/ARB in all patients with LN
- Statins if LDL-cholesterol > 115 mg/dl
- Avoid estrogen-containing contraceptive pill
- Stop smoking
- Prevention of GC-induced bone loss
- Immunization (flu, HPV, *Strept. Pneumoniae*)