ADULT LUPUS -

CLINICAL INSIGHTS AND THERAPEUTIC CHALLENGES

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DISCLOSURES

Professor Isenberg has consulted for the companies:-

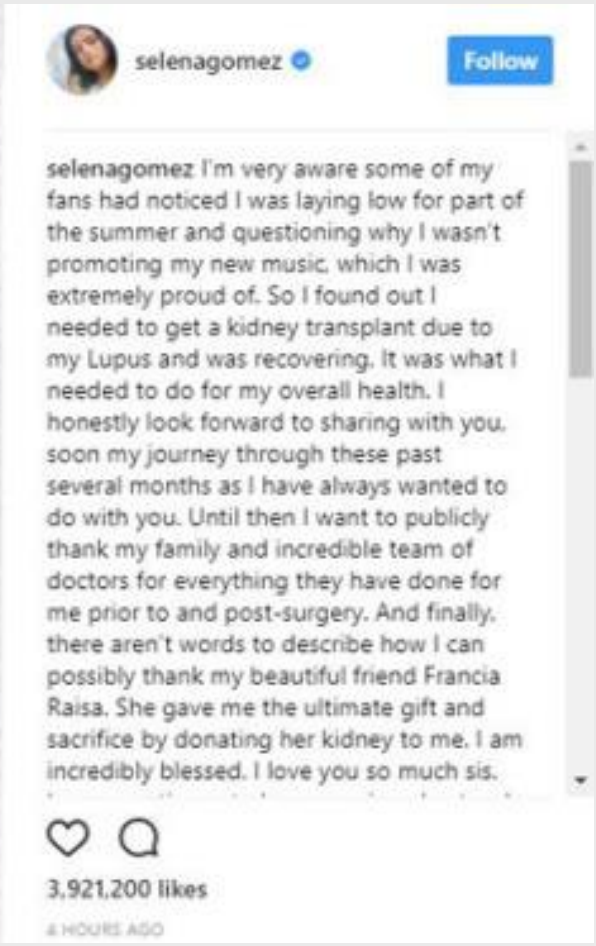
Merck Serono, Pfizer, Glaxo Smith Kline,

ImmuPharma, UCB, GSK, Celgene and Eli Lilly.

The honoraria offered are passed onto a local arthritis charity.

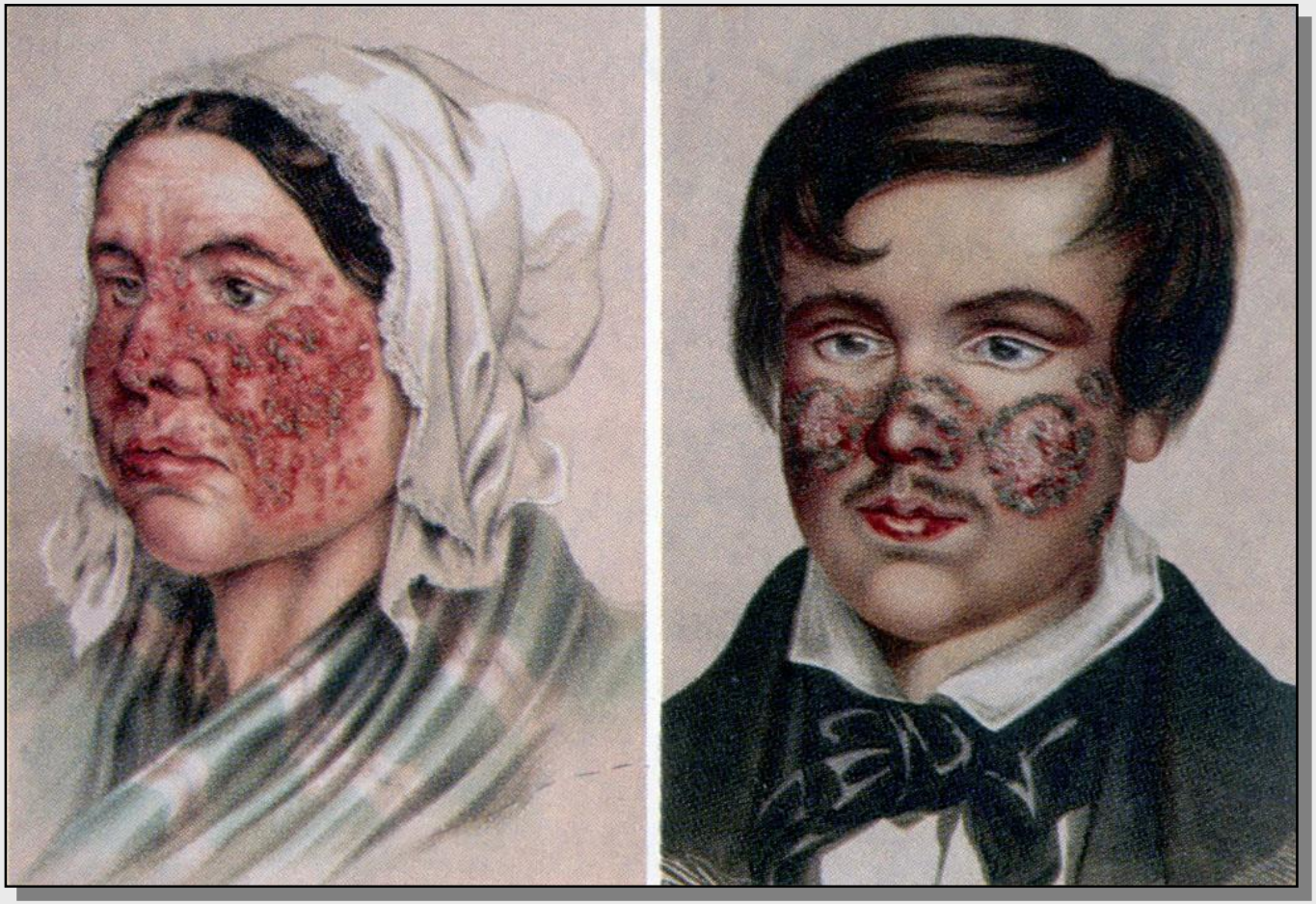
LUPUS STREET

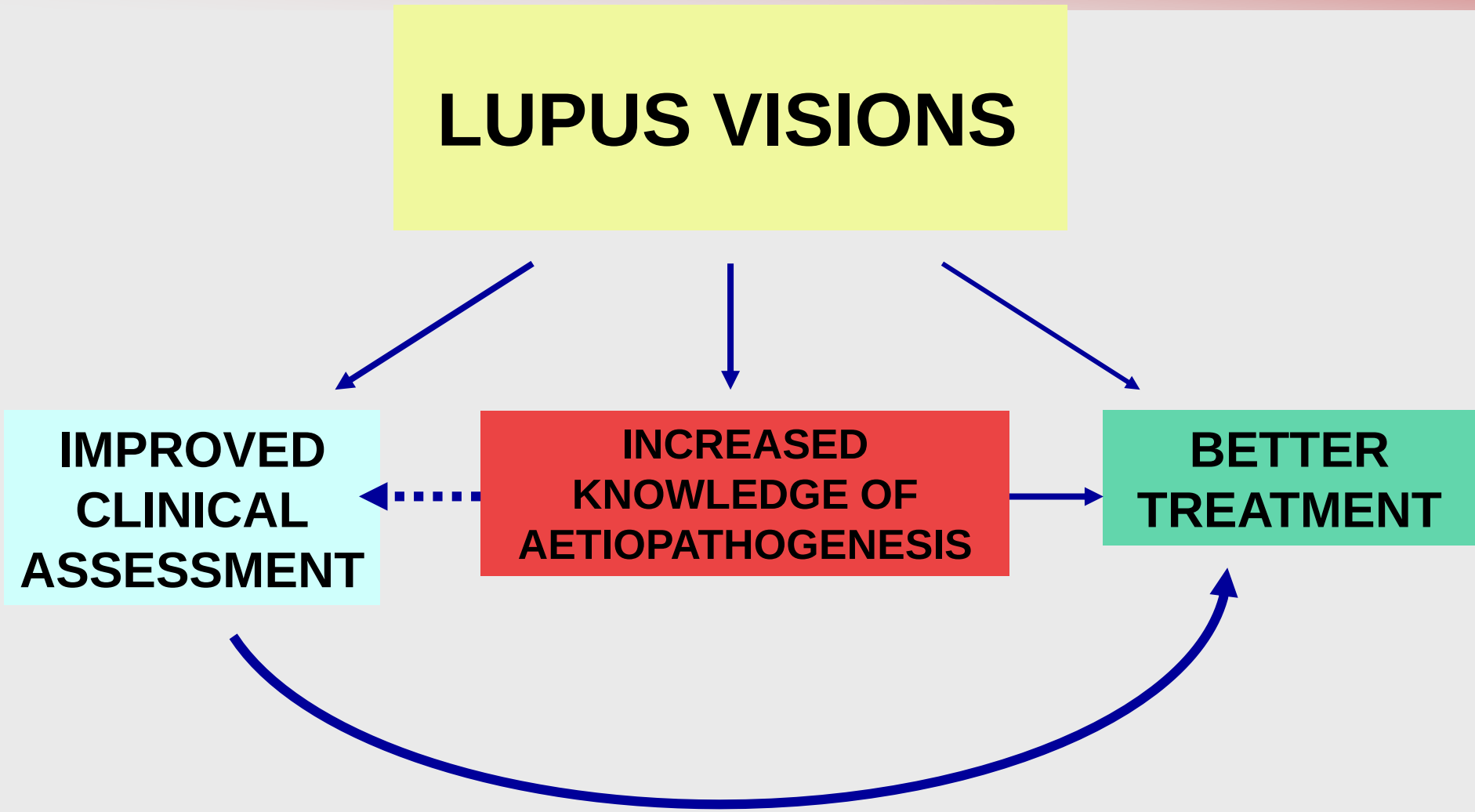
SELENA GOMEZ HAS A KIDNEY TRANSPLANT BECAUSE OF LUPUS NEPHRITIS

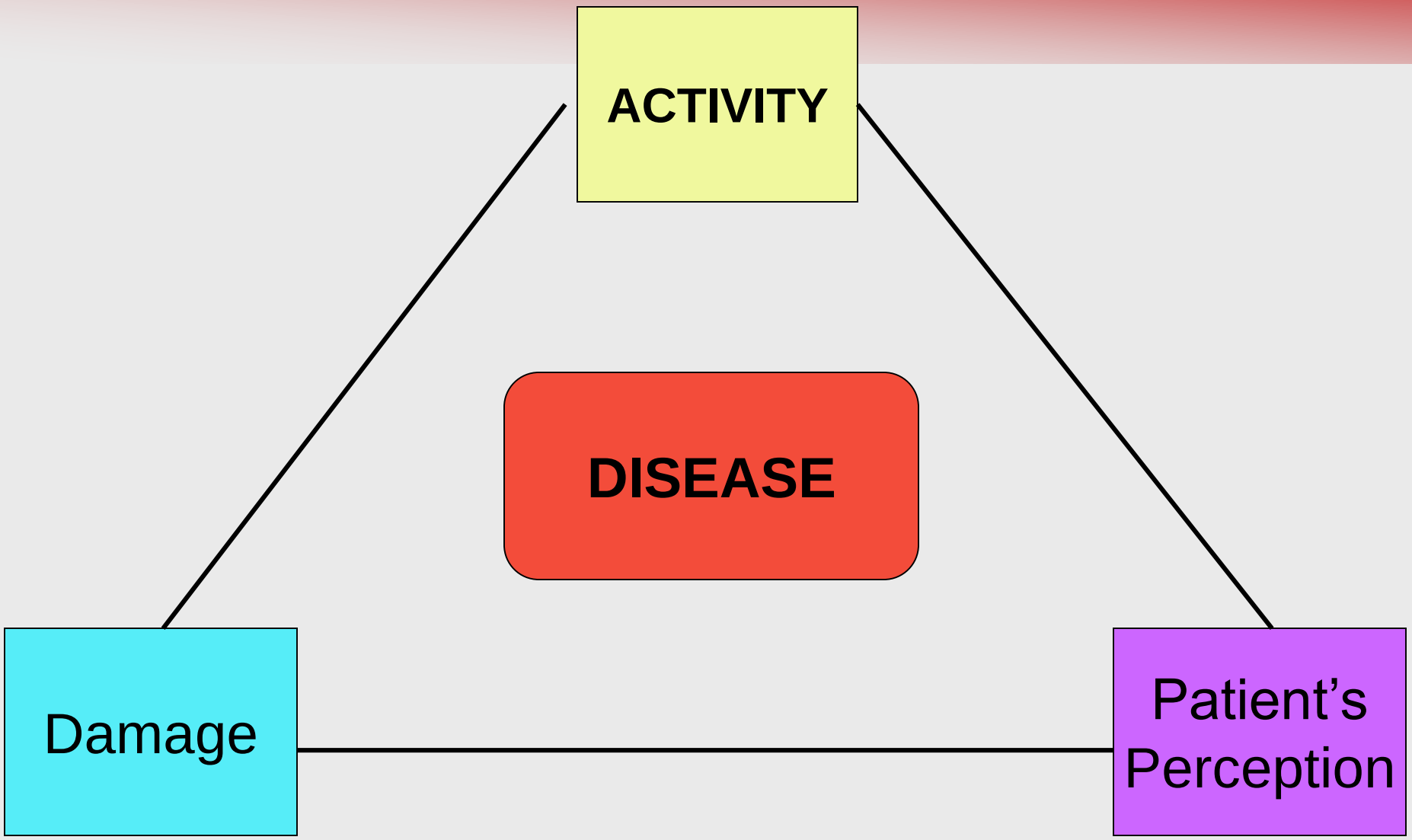


LUPUS – IT'S EVERYWHERE!

History of Lupus




LUPUS VISIONS
IMPROVED CLINICAL ASSESSMENT
INCREASED KNOWLEDGE OF AETIOPATHOGENESIS
BETTER TREATMENT


ACTIVITY
DISEASE
Damage
Patient's Perception

A FEW WORDS ABOUT MONITORING (1)

- **See SLE patients regularly**
  - **active disease – every 1-3 mn**
  - **inactive disease – every 6-12 mn**

- **Close monitoring of drugs is necessary especially:**
  - **Immunosuppression and steroids**
  - **HCQ [eye checks but? how often]**

A FEW WORDS ABOUT MONITORING (2)

- **Serological awareness**
  - **anti Ro/La – photosensitivity/heart block**
  - **anti-phospholipid abs – clots/miscarriage**
  - **↑ dsDNA – renal disease**

- **Watch for co-morbidities**
  - **Atherosclerosis**
  - **Osteoporosis/avascular necrosis**
  - **Infection**
  - **Cancer**

ANTI-ENA ANTIBODIES – WHERE DID THE NAMES COME FROM?

- **Anti-Sm = Smith**
- **Anti-Ro = Robair**
- **Anti-La = Latimer**

TREATMENT ALGORITHMS IN SLE (2)

EXAMPLES

	1
	Constitutional symptoms
1st Line	**HCQ/CS/ Immunomodulation**
2nd Line	**MMF**
3rd Line	**Rituximab/ Belimumab**

TREATMENT ALGORITHMS IN SLE (2)

EXAMPLES

	1	2
	Constitutional symptoms	Widespread DLE
1st Line	HCQ/CS/ Immunomodulation	HCQ ± CS
2nd Line	MMF	ADD AZA
3rd Line	Rituximab/ Belimumab	AZA → MMF or MTX

TREATMENT ALGORITHMS IN SLE (2)

EXAMPLES

	1	2	3
	Constitutional symptoms	Widespread DLE	Polyarthritis
1st Line	HCQ/CS/ Immunomodulation	HCQ ± CS	HCQ + CS
2nd Line	MMF	ADD AZA	ADD MTX
3rd Line	Rituximab/ Belimumab	AZA → MMF or MTX	Rituximab

TREATMENT ALGORITHMS IN SLE (2)

EXAMPLES

	1	2	3	4
	Constitutional symptoms	Widespread DLE	Polyarthritis	Thrombo-cytopenia
1st Line	HCQ/CS/ Immunomodulation	HCQ ± CS	HCQ + CS	CS ± HCQ
2nd Line	MMF	ADD AZA	ADD MTX	AZA/MMF
3rd Line	Rituximab/ Belimumab	AZA → MMF or MTX	Rituximab	Rituximab/ IV Cyclo/ Ivlg

TREATMENT ALGORITHMS IN SLE (3)

EXAMPLE

	5
	Lupus APS arterial thrombolysis
1st Line	Warfarin/ LMW Hep IHCU
2nd Line/ Induction	Add aspirin/ Dipyriadamole/ Platelet agg inhib
3rd Line	/

TREATMENT ALGORITHMS IN SLE (3)

EXAMPLE

	5	6
	Lupus APS arterial thrombolysis	**Mononeuritis Multiplex**
1st Line	**Warfarin/ LMW Hep IHCU**	**CS + IV Cyclo**
2nd Line/ Induction	**Add aspirin/ Dipyriadamole/ Platelet agg inhib**	**Add Rituximab or IVIG/PE**
3rd Line	**/**	**/**

TREATMENT ALGORITHMS IN SLE (3)

EXAMPLE

	5	6	7
	Lupus APS arterial thrombolysis	**Mononeuritis Multiplex**	**Nephritis III/IV**
1st Line	**Warfarin/ LMW Hep IHCU**	**CS + IV Cyclo**	**CS + MMF**
2nd Line/ Induction	**Add aspirin/ Dipyriadamole/ Platelet agg inhib**	**Add Rituximab or IVIG/PE**	**IV Cyclo**
3rd Line	**/**	**/**	**Add Rituximab**

TREATMENT ALGORITHMS IN SLE (3)

EXAMPLE

	5	6	7	8
	Lupus APS arterial thrombolysis	**Mononeuritis Multiplex**	**Nephritis III/IV**	**Nephritis V**
1st Line	**Warfarin/ LMW Hep IHCU**	**CS + IV Cyclo**	**CS + MMF**	**CS + MMF**
2nd Line/ Induction	**Add aspirin/ Dipyriadamole/ Platelet agg inhib**	**Add Rituximab or IVIG/PE**	**IV Cyclo**	**→ AZA/IV Cyclo or Rituximab**
3rd Line	**/**	**/**	**Add Rituximab**	**/**

TREAT TO TARGET (1)

1. **The treatment target of SLE should be remission of systemic symptoms and organ manifestations/lowest possible disease activity – measured by a validated activity index and/or organ-specific markers.**

2. **Prevention of flares (especially severe flares) is a realistic target and should be a therapeutic goal.**

[Van Vollenhoven et al. Ann Rheum Dis 2014; 73: 958]

TREAT TO TARGET (2)

3. It is not recommended that the treatment in clinically asymptomatic patients be escalated based solely on stable/persistent serological activity.

4. Since damage predicts subsequent damage and death, prevention of damage accrual should be a major therapeutic goal in SLE.

TREAT TO TARGET (3)

5. **Factors negatively influencing health-related quality of life [HRQOL] eg fatigue or pain, should be addressed in addition to control of disease activity and damage prevention.**

6. **Early recognition and treatment of renal involvement in lupus is strongly recommended.**

TREAT TO TARGET (4)

7. For lupus nephritis following induction therapy at least 3 years of immunosuppressive maintenance therapy is recommended.

8. Lupus maintenance treatment should aim for the lowest glucocorticoid dosage needed to control disease (and if possible withdrawn completely).

TREAT TO TARGET (5)

9. Prevention and treatment of APS related morbidity should be a therapeutic goal.

10. Irrespective of other treatments consideration should be given to using anti-malarials.

11. Relevant therapies adjunctive to any immunomodulation should be considered to control co-morbidity in SLE.

FLARE RATES USING BILAG 2004 INDEX

During Jan 2014 – Dec 2014

323 patients were seen on at least 3 occasions

135 patients had a flare

Severe	Moderate	Mild	No Flares
1 ‘A’ at least	2 ‘B’s	1 ‘B’ or 3 ‘C’s	
8.4%	9.3%	35%	47%

Ciang, Isenberg. Rheumatology 2016; 55: S169

A FEW WORDS ABOUT ALTERNATIVE EXPLANATIONS FOR CLINICAL FEATURES IN LUPUS (1)

A)

CONCOMITANT DISEASE IN UCL COHORT (1978 – 2018) (n = 700)	
Hypothyroid	8%
Sjögren's	7%
Antiphospholipid antibody syndrome	7%
Myositis	4%
Diabetes	3%

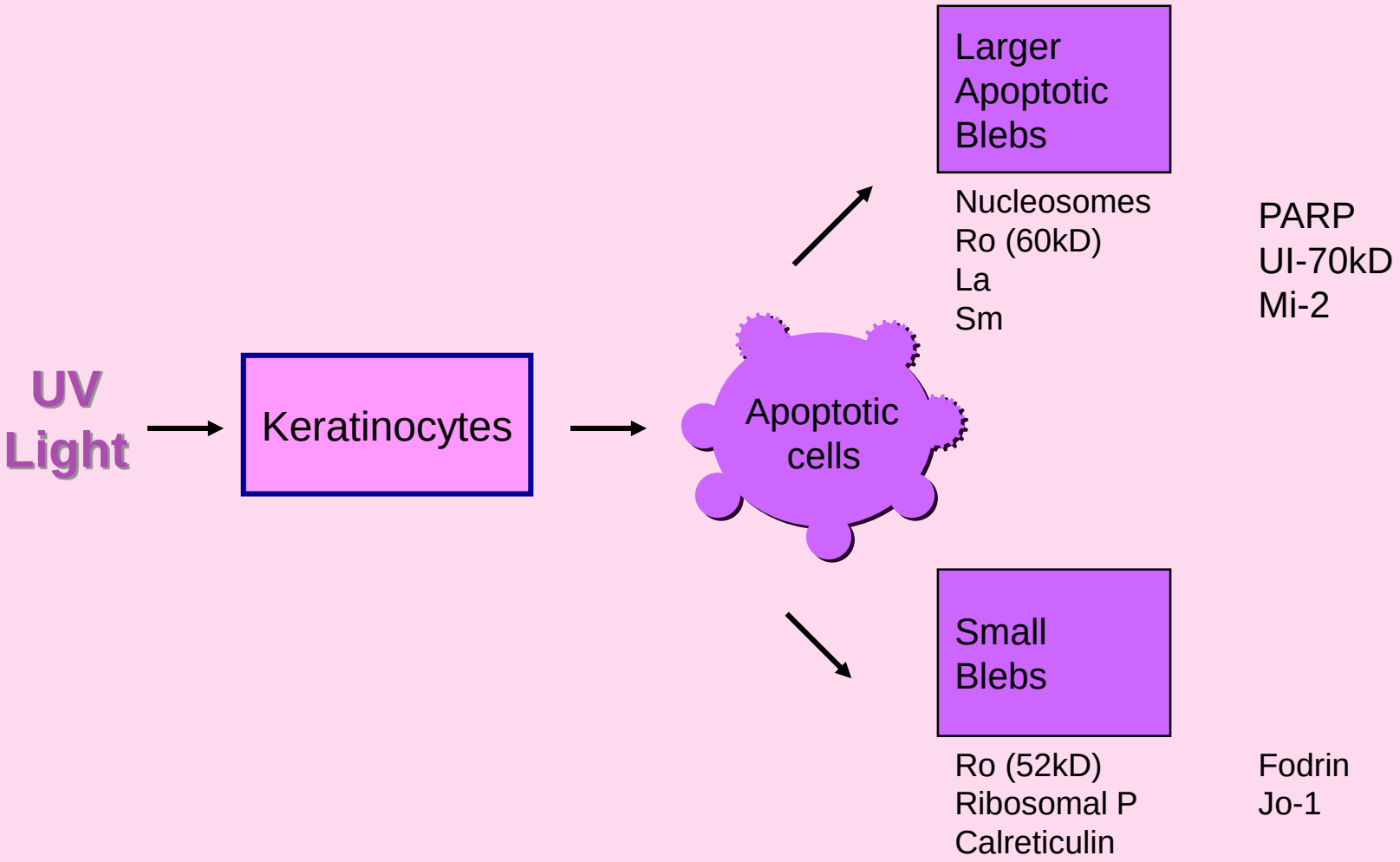
TREATMENT ALGORITHMS IN SLE (1)

STUDY INVOLVED

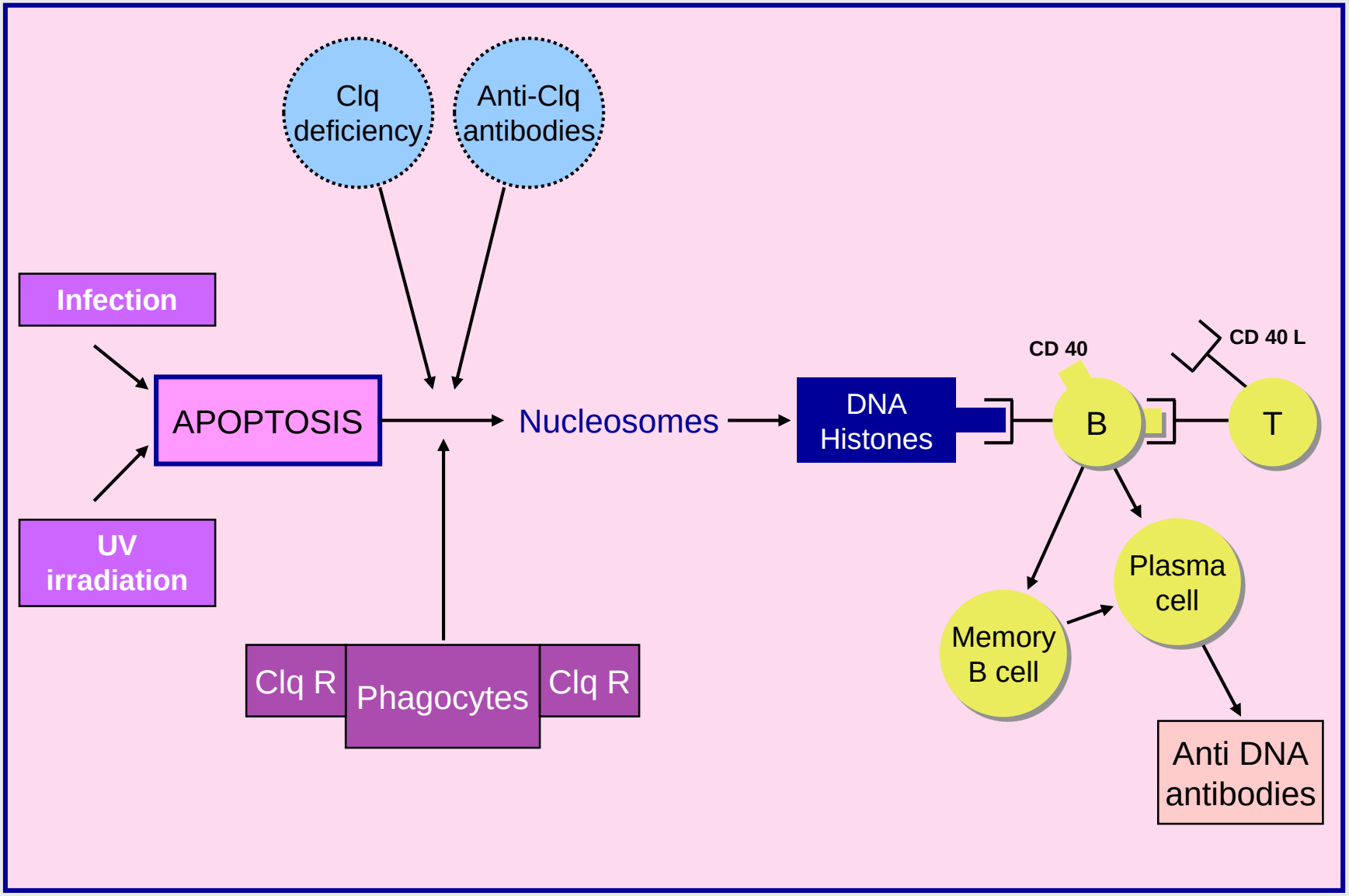
- 69 SLE experts approached (54% responded)
- Each respondent sent 16 scenarios to suggest how to treat
- Algorithms constructed and agreement determined ($\geq$ 50% respondents indicating $\geq$ 70% agreement)

Muangchan et al. Arthritis Care Res 2016; 67: 1232

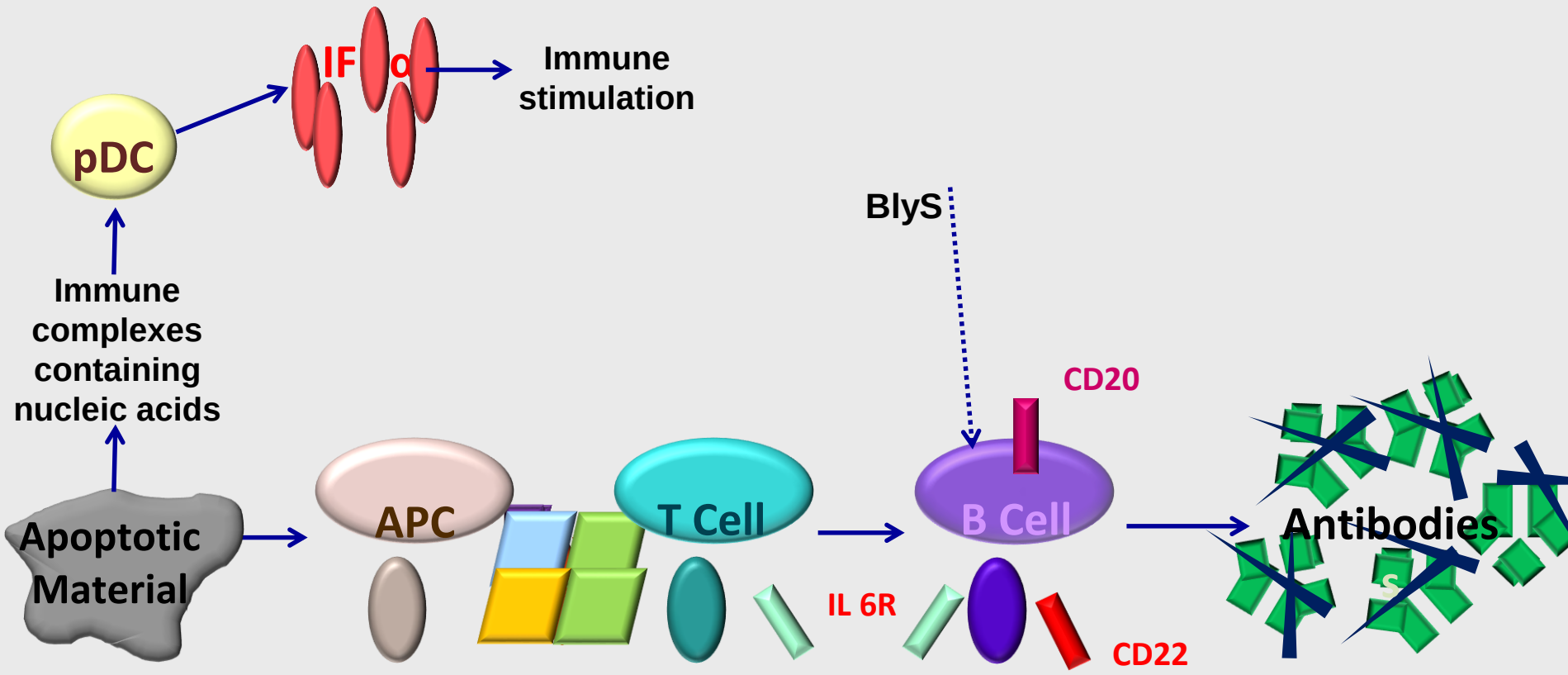
CELL DEATH


UV Light
Keratinocytes
Apoptotic cells
Larger Apoptotic Blebs
Nucleosomes
Ro (60kD)
La
Sm
PARP
UI-70kD
Mi-2
Small Blebs
Ro (52kD)
Ribosomal P
Calreticulin
Fodrin
Jo-1

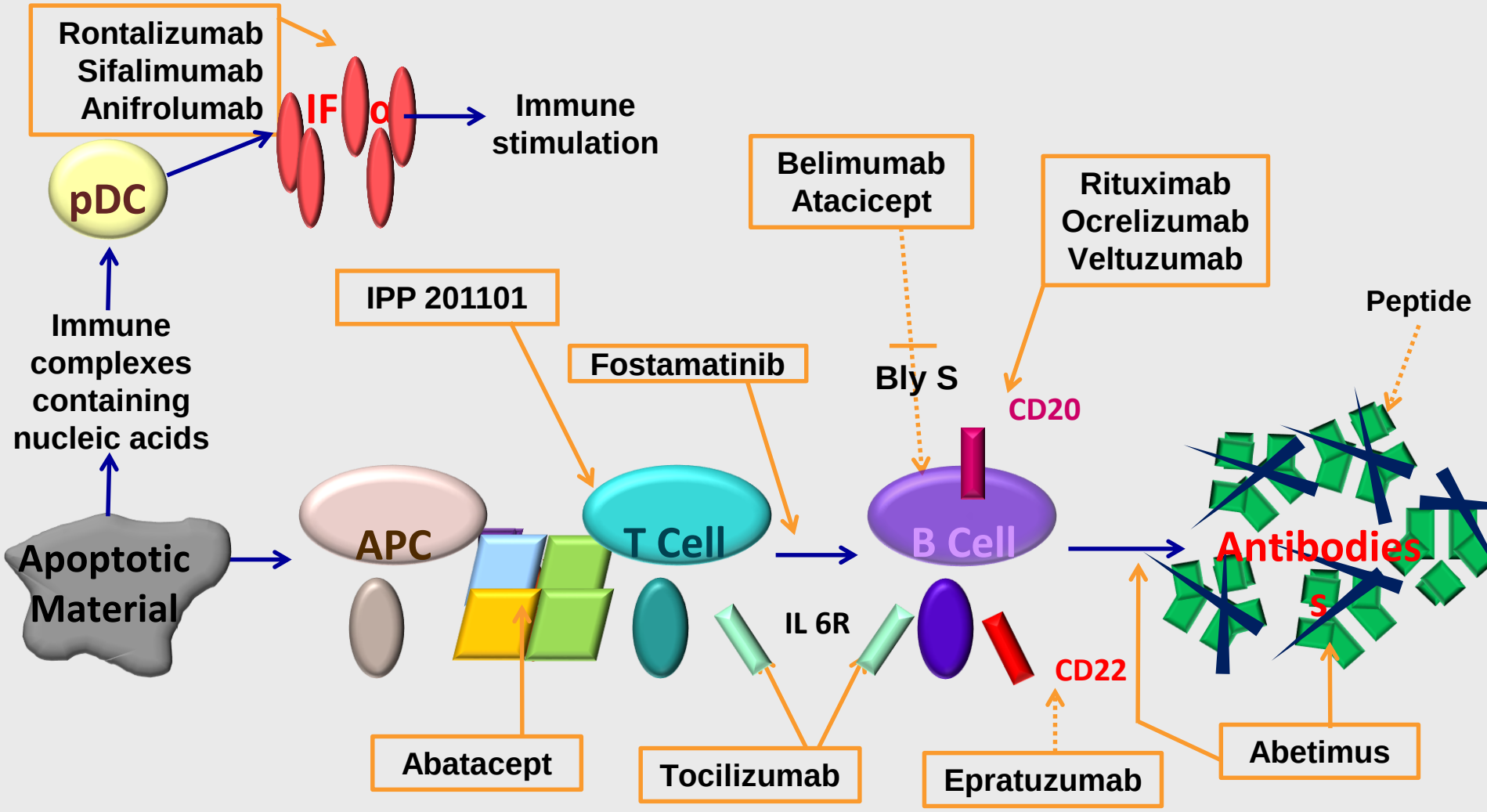
CELL DEATH


Clq deficiency
Anti-Clq antibodies
Infection
UV irradiation
APOPTOSIS
Nucleosomes
DNA Histones
CD 40
CD 40 L
B
T
Plasma cell
Memory B cell
Anti DNA antibodies
Clq R
Phagocytes
Clq R

TARGET PATHWAY FOR SLE THERAPIES



SOME TARGETED THERAPIES FOR SLE



OVERVIEW – BIOLOGIC TREATMENT IN LUPUS -1-

BIOLOGIC	TRIAL RESULTS	CURRENT 'REAL-WORLD USE'
B-CELL BLOCKING **Rituximab (anti-CD20)**	**EXPLORER - FAILED (non-renal)** **LUNAR - FAILED (renal)** **(some clinical and serological benefits noted in post-hoc analyses)**	**Widely-used, most physicians have found this drug to be of benefit.**
Epratuzumab (anti-CD22)	**EMBODY 1 – FAILED** **EMBODY 2 – FAILED**	**UCB are most unlikely to proceed to further studies.**
APC – T-CELL BLOCKING **Abatacept**	**MMF+ Abatacept – FAILED** **ACCESS - FAILED (Cyclophos + Abatacept)**	**Another trial of Abatacept and MMF is underway**


ELVIS
HEARTBREAK
HOTEL
I WAS THE ONE
RCA
COLLECTORS'
SERIES
LIMITED EDITION


HOTEL

HEARTBREAK HOTEL – ELVIS PRESLEY

Well, since my baby left me

Well, I found a new place to dwell

Well, it's down at the end of Lonely Street

At Heartbreak Hotel

Where I'll be—where I get so lonely, baby

Well, I'm so lonely

I get so lonely, I could die

Well, those lupus trials failed

Another one bites the dust

The wolves of hell are waiting for me

In the Heartbreak Hotel

Where I'll be…in good company

Yes in good company

And so depressed cos my patients could die

OVERVIEW – BIOLOGIC TREATMENT IN LUPUS -2-

BIOLOGIC	TRIAL RESULTS	CURRENT TRIALS & 'REAL-WORLD USE'
BLOCKING B-CELL ACTIVATING FACTORS **Belimumab (anti BAFF/BLyS)**	**BLISS-52 met its primary endpoint with both doses.** **BLISS-76 met its primary endpoint with higher dose.**	**Increasingly used in USA and Europe, but not UK where NICE have not approved it.**
Tabalimumab (anti-BAFF)	**ILLUMINATE 1 – FAILED** **ILLUMINATE 2 – Met its primary endpoint**	**Eli-Lilly have decided not to proceed to any further studies.**
Blisibimod (anti-BAFF)	**In PEARL-SC (phase II) post-doc analysis of SR1-8 and high disease activity the drug -200mg wk - showed benefit.**	**Phase III trial (CHABLIS) – FAILED.**
Atacicept (anti-BAFF and APRIL)	**APRIL-SLE safety committee prematurely and incorrectly terminated the higher dose arm; but ITT showed this dose reduced the numbers of flares and time to first flare.**	**Phase II trial (ADDRESS) of patients with active lupus – SUCCESSFUL.**

UPDATE ON RITUXIMAB USE IN SLE (1)

1) Recommended in the ACR and EULAR guidelines for the treatment of lupus nephritis

2) Approved in the UK by NHS England

3) Widely used for many aspects of lupus

4) No help in approximately 10% of patients

5) Be aware of hypogammaglobinaemia and allergic responses

UPDATE ON RITUXIMAB USE IN SLE (2)

SPEED OF ONSET:-

1)	Anaemic/thrombocytopenia	-	within 2 weeks
2)	Arthritis	-	1 – 2mn
3)	Pleurisy/pericarditis	-	1 – 2mn
4)	Skin	-	variable
5)	Renal	-	maybe several months

RITUXIMAB (RTX) IN SLE – UCL EXPERIENCE (UPDATE) – 3 -

	1st RTX cycle	All RTX cycles
	%	%
% pts ↓ dsDNA ≥ 50% or normalisation	38.2	37.7
% pts with ↑ in C3 ≥ 25% or normalisation	36.5	31.8
% loss of all BILAG As and Bs	43	42
% loss of some but not all BILAG As and Bs	29	27
% with no response	28	30
% successful $CD19^+$ lymphocyte depletion	94	92

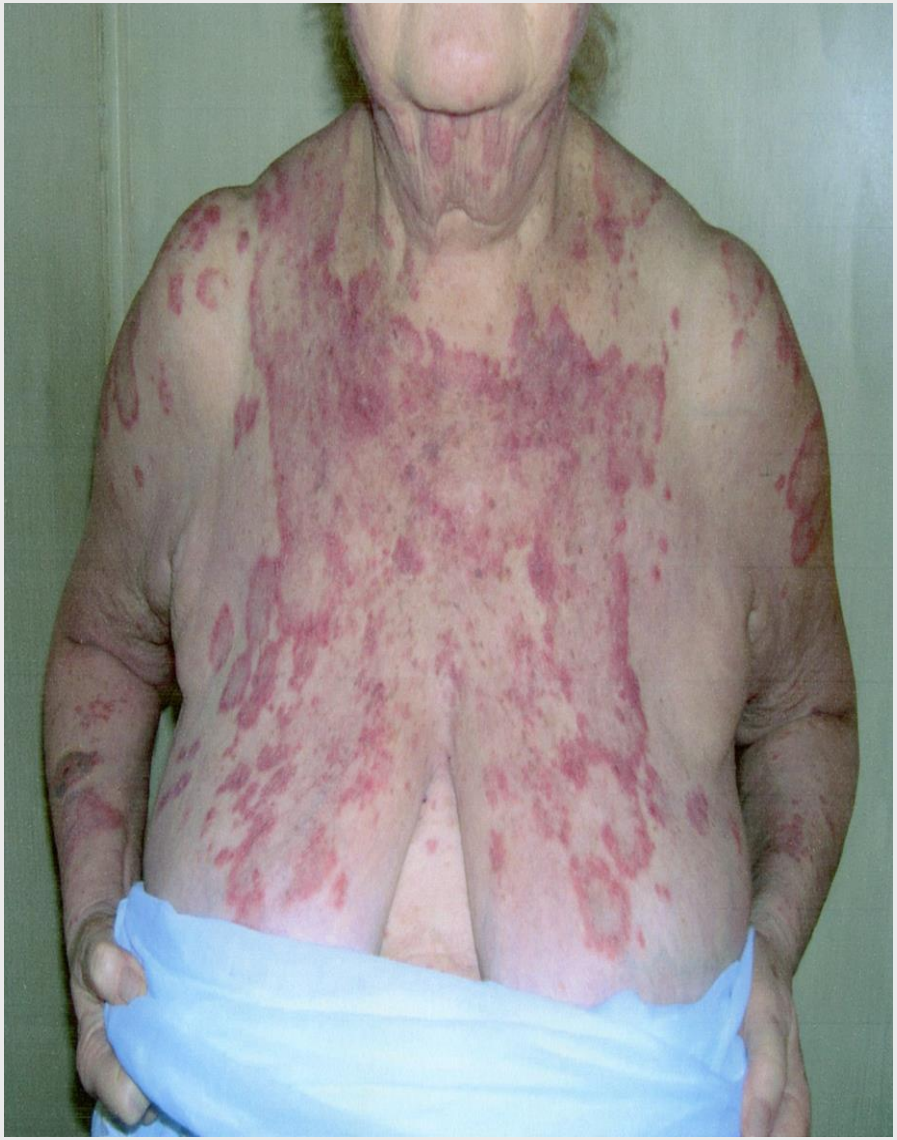
RITUXIMAB (RTX) IN SLE (n = 115) – UCL EXPERIENCE (UPDATE) – 4 -

Adverse Event	1ST RTX cycle	All RTX cycles
Severe infections	8	13
Hypersensitivity reactions	3	13
Hypogammaglobulinaemia	27	53

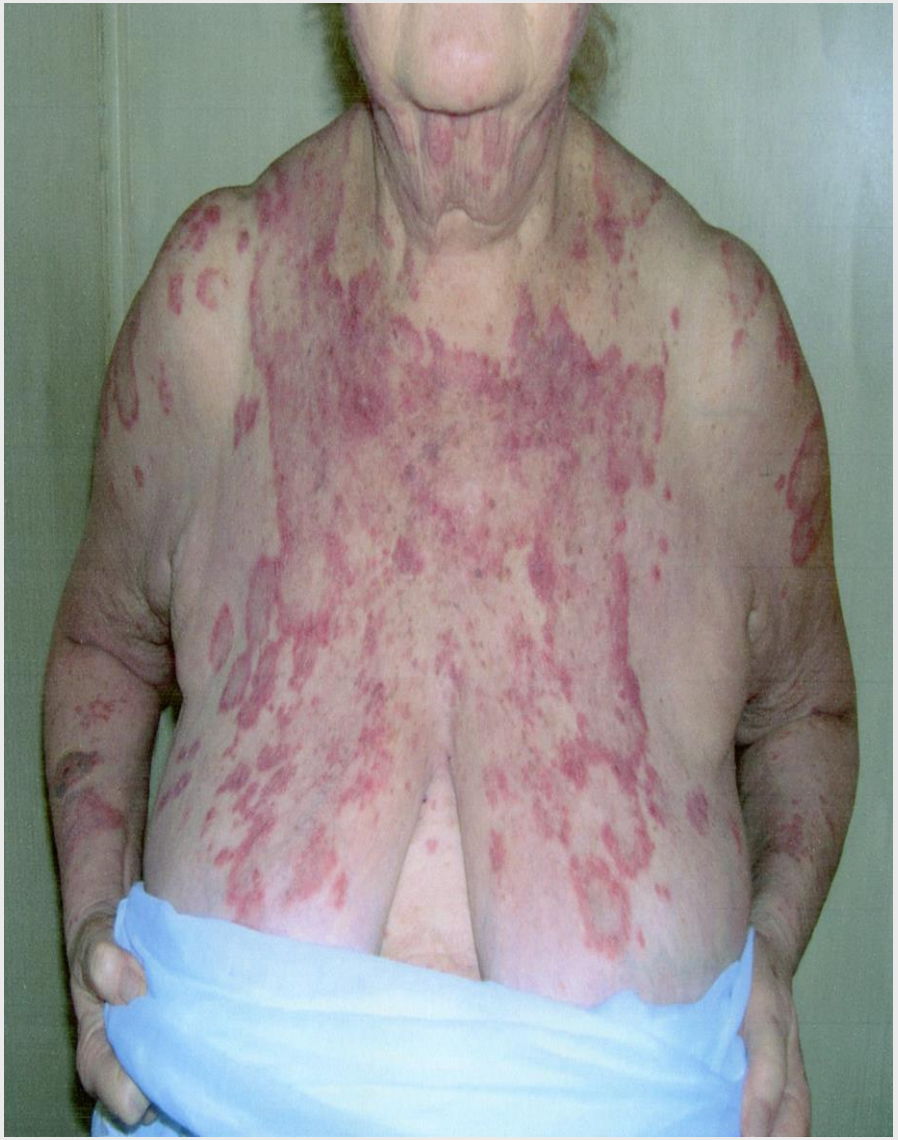
Nb: During the follow-up period [up to 15 years] 5 patients had at least 1 CVS event and 11 have died.

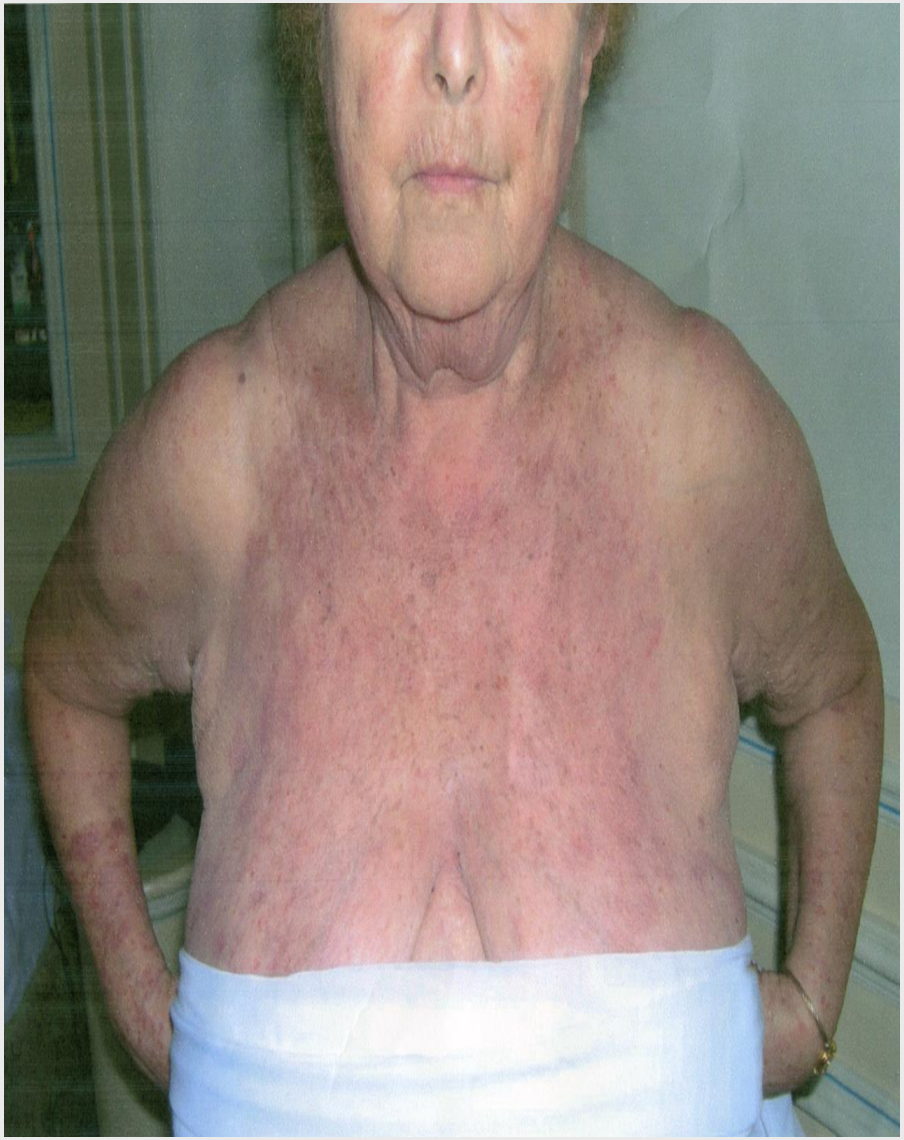
Aguiar, Araujo, Papoila, Alves, Isenberg. Arthritis Care Res 2017; 69: 257-62

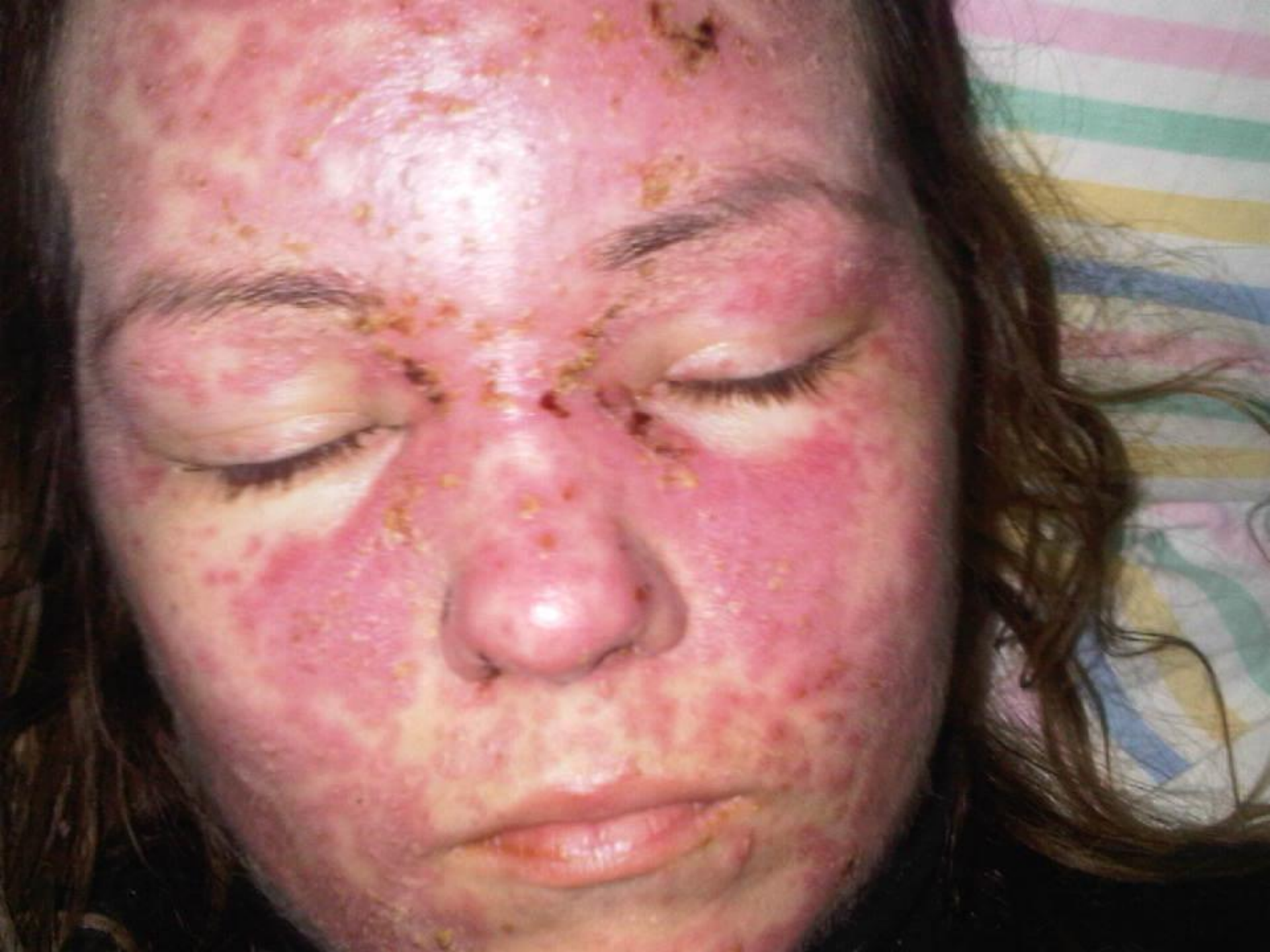
Severe Sub-acute Cutaneous Lupus - Before B cell Depletion

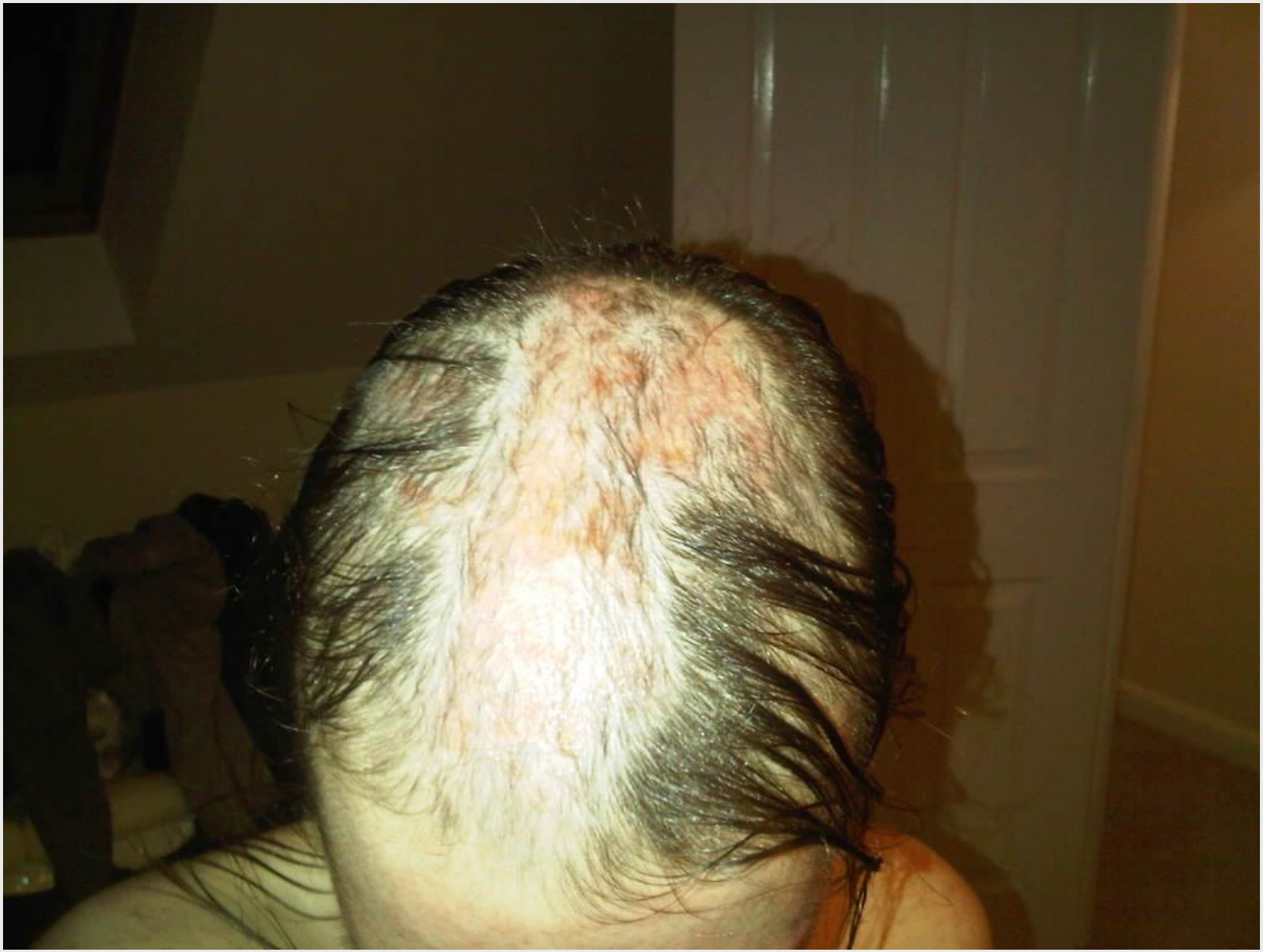


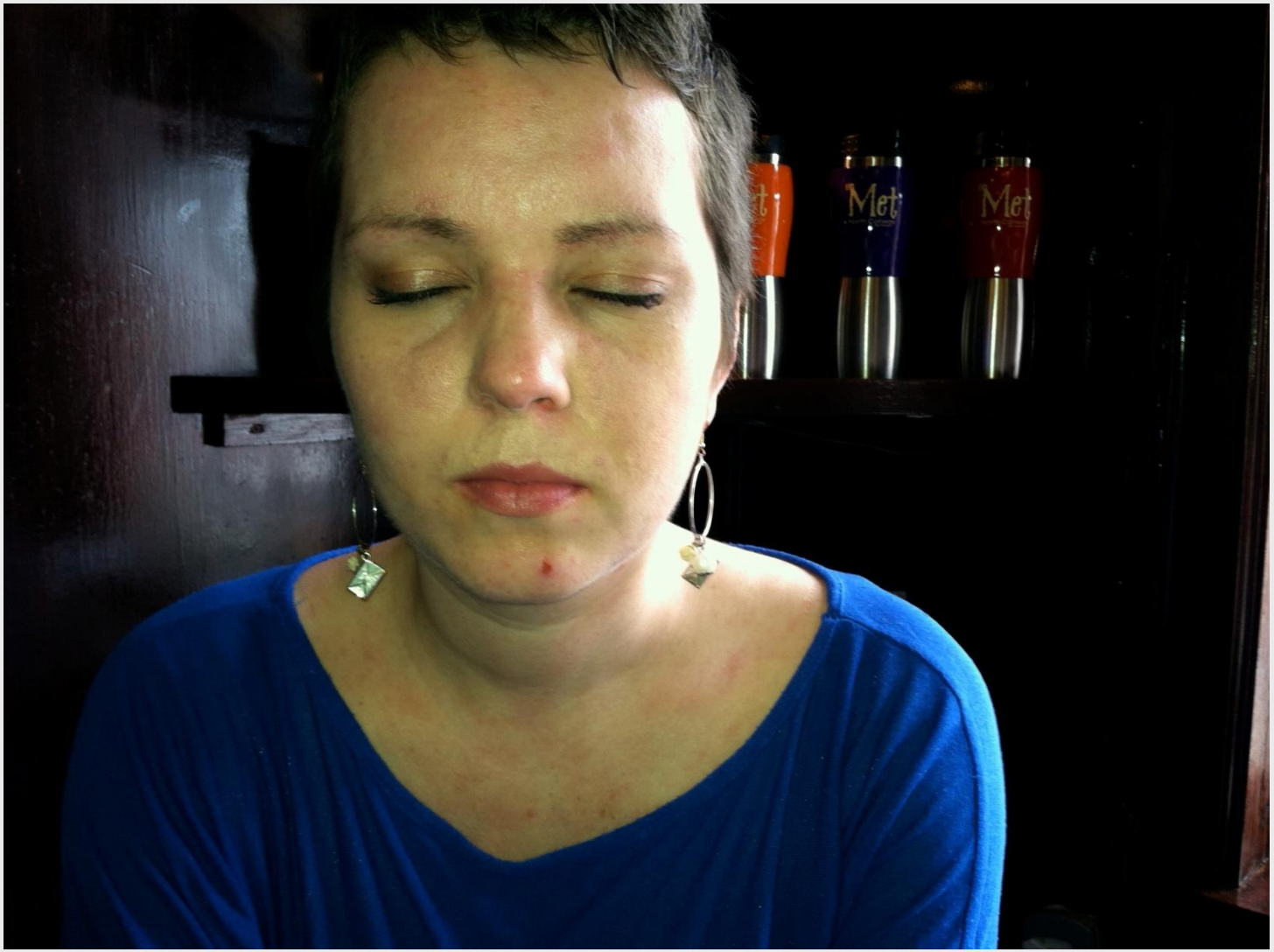
Severe Sub-acute cutaneous Lupus Treated with B cell Depletion - Before and 1 Month Afterwards









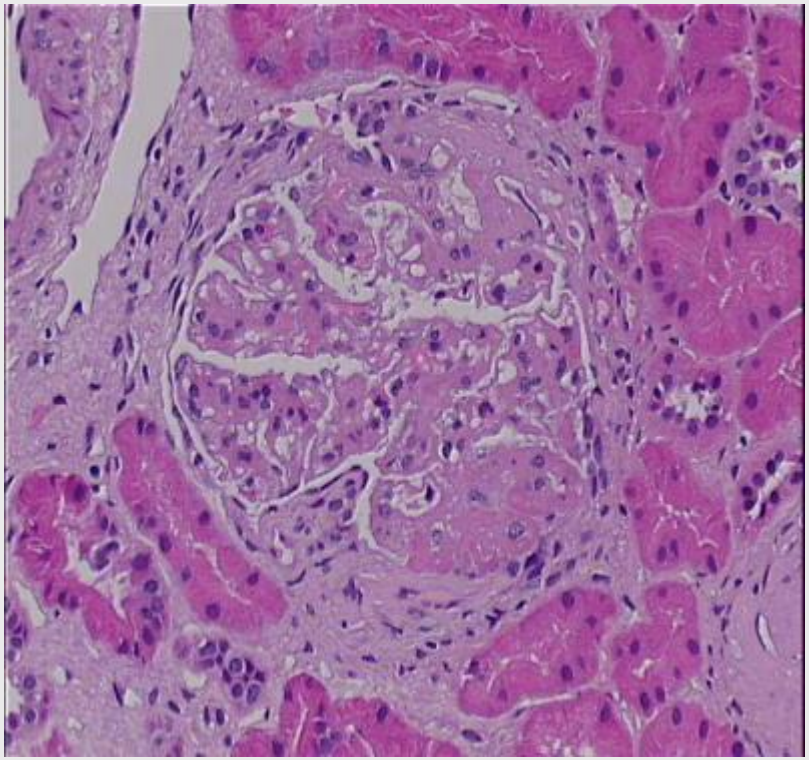


B-CELL DEPLETION USING RITUXIMAB IN CUTANEOUS LUPUS

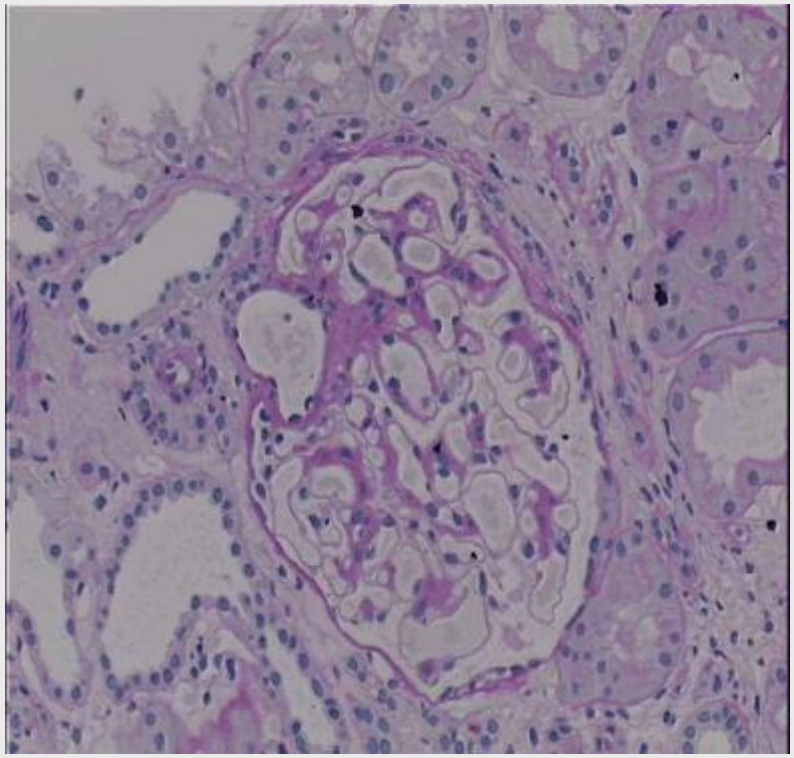
COMPLETE RESPONDER [LOST BILAG A/B STATUS]			
	n =	6/12	1 yr
Acute cutaneous lupus (ACLE)	23	35%	57%
Subacute cutaneous lupus (SCLE)	6	33%	33%
Chronic cutaneous lupus (CCLE)	12	42%	46%
Non-specific lupus (NSLE)	11	46%	60%

Costa, Aguirre-Alastuey, Isenberg, Saracino JAMA-Dermatology. In press

Renal biopsy appearance



Before



After

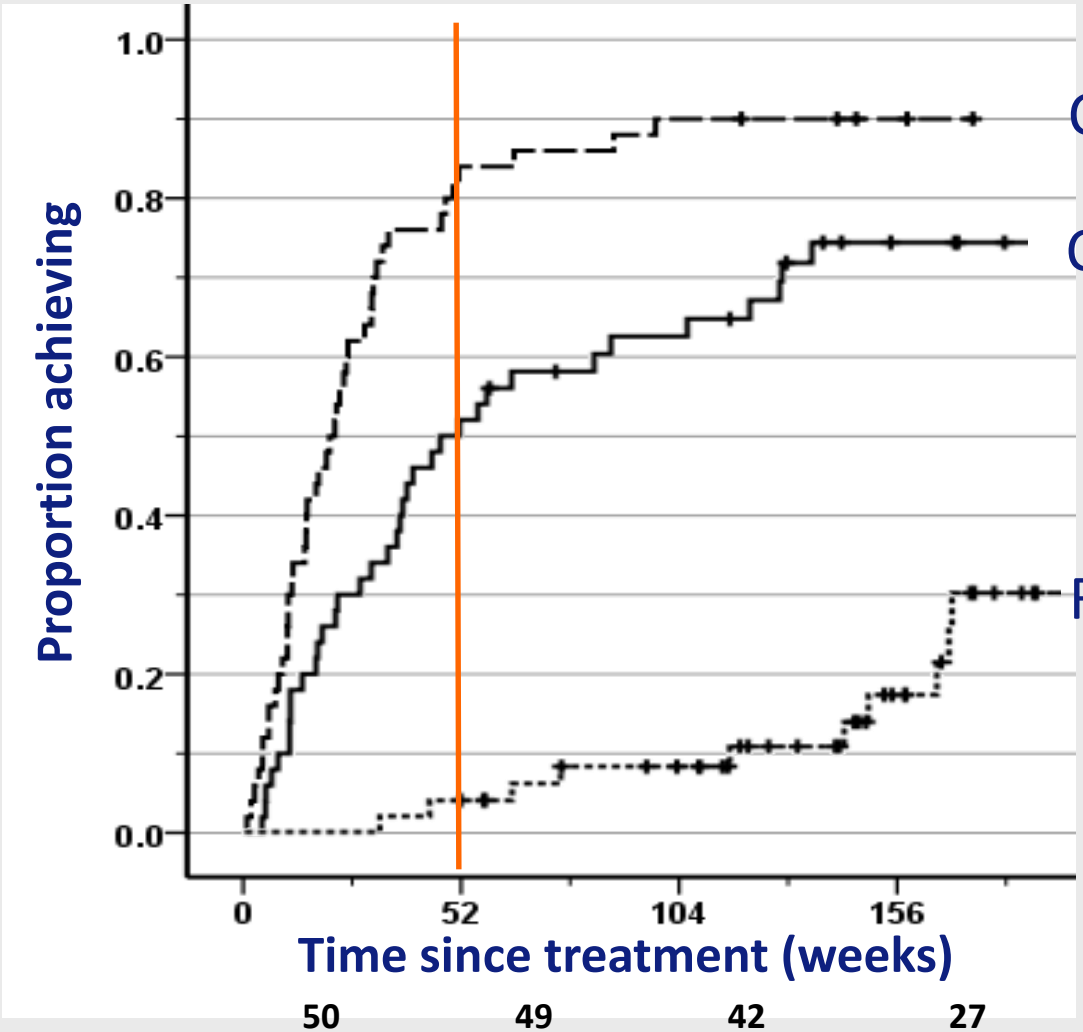
With thanks to Professor Ronald Van Vollenhoven

Treatment regime - Rituxilup

- Steroid avoiding regime
- Used in all new and relapsing lupus who are not already on steroids and who do not have cerebral lupus
- Very low toxicity
- Established as our first line treatment protocol

Condon et al. Annals Rheum Dis. 2013. 72:1280-6

Time to remission and relapse



In CR:

- 12 wks 9 (18%)
- 26 wks 16 (32%)
- 52 wks 26 (52%)

Condon et al Ann Rheum Dis. 2013; 72: 1280-6.

Early B-cell Depletion – Long-Term Follow-Up – 1-

- **16 SLE patients treated at diagnosis in UCLH since 2008**

- **Each matched with 3 other patients treated conventionally from the cohort for:**

ethnicity

sex

age

clinical features

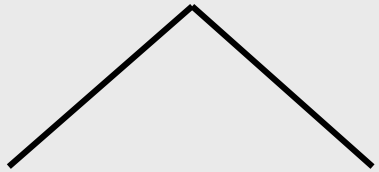
disease duration

Gracia-Tello et al. Lupus Sci Med 2017; 4: e000182

Early B-cell Depletion – Long-Term Follow-Up – 4-

Results:-

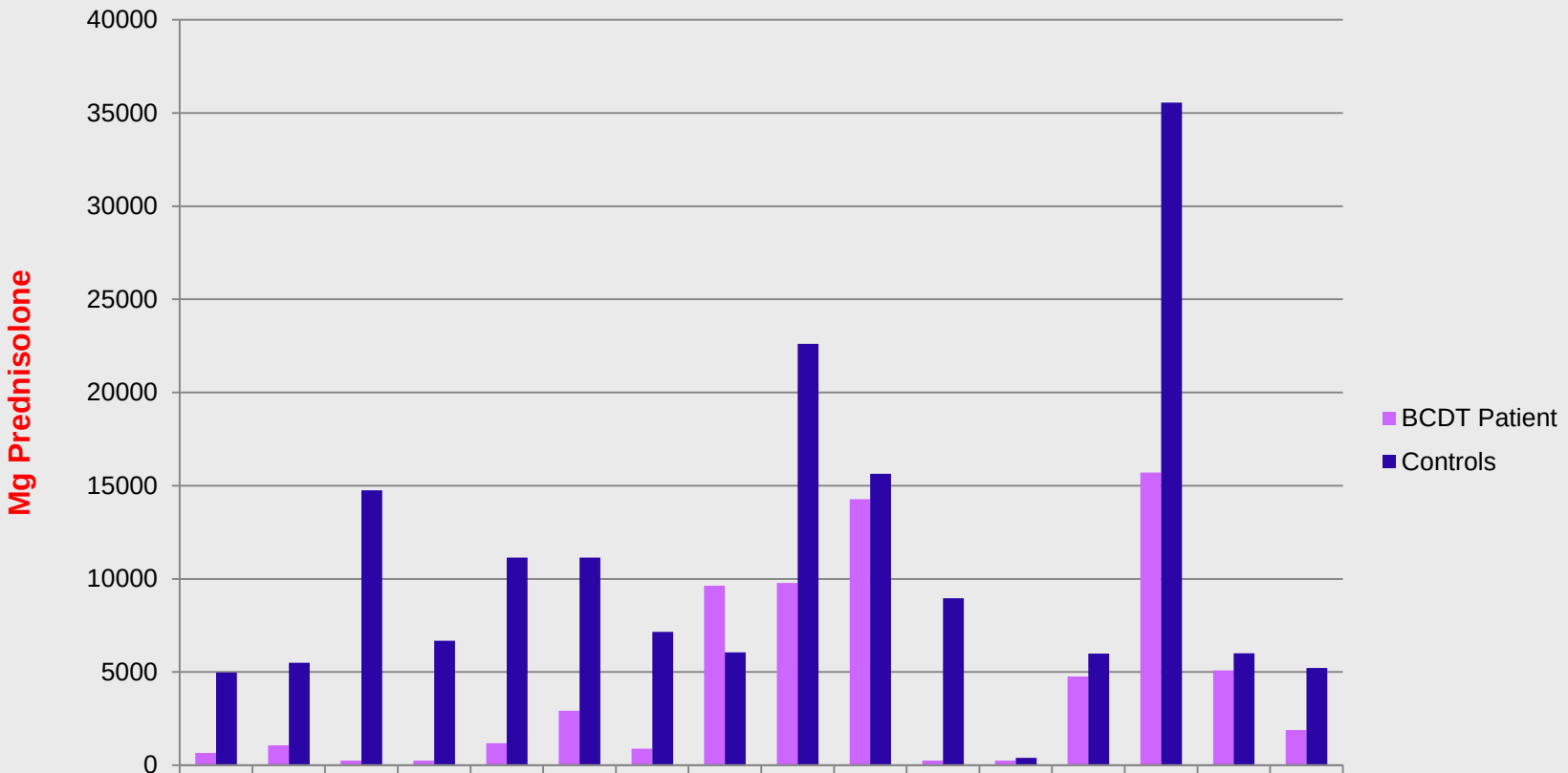
- **All Rituximab treated patients achieved B-cell depletion**
- **Clinical Flares [new BILAG A or B]**



BCDT **Conventional Treatment**

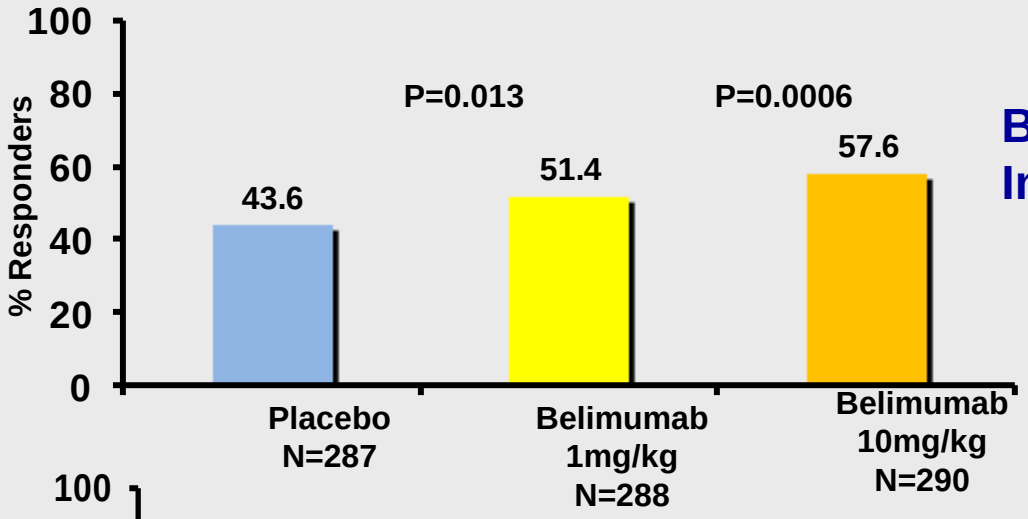
Overall	50%	70%
Numbers of flares	3.75 (SD = 4.0)	4.27 (SD = 4.0)

Steroid burden in newly-diagnosed SLE patients

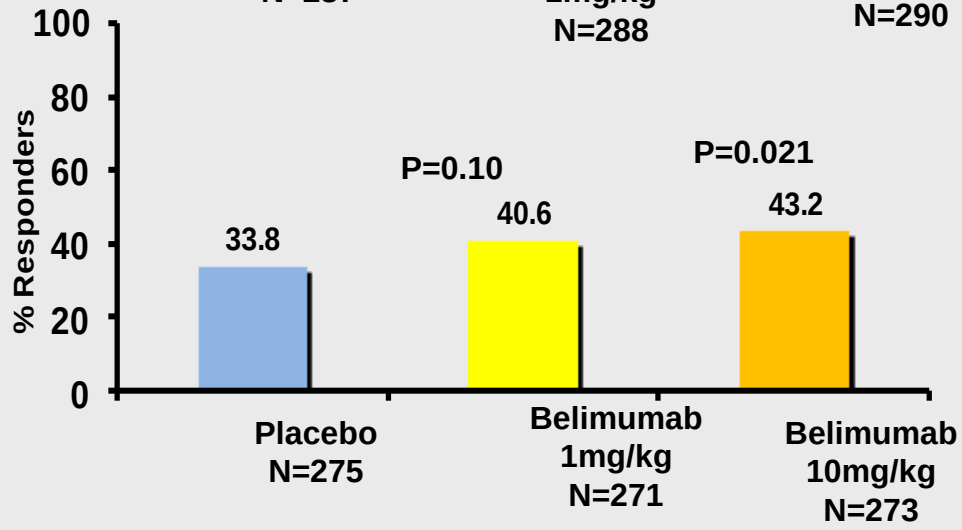


	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
BCDT Patient	659	1071	250	250	1186	2924	884	9640	9773	14281	250	250	4758	15695	5088	1897
Controls	4981	5501	14746	6679	11134	11134	7155	6064	22610	15644	8960	399	5994	35555	5999	5217

UPDATE ON BENLYSTA (1)



BLISS-52:SLE Responder Index*: % Response at Week 52



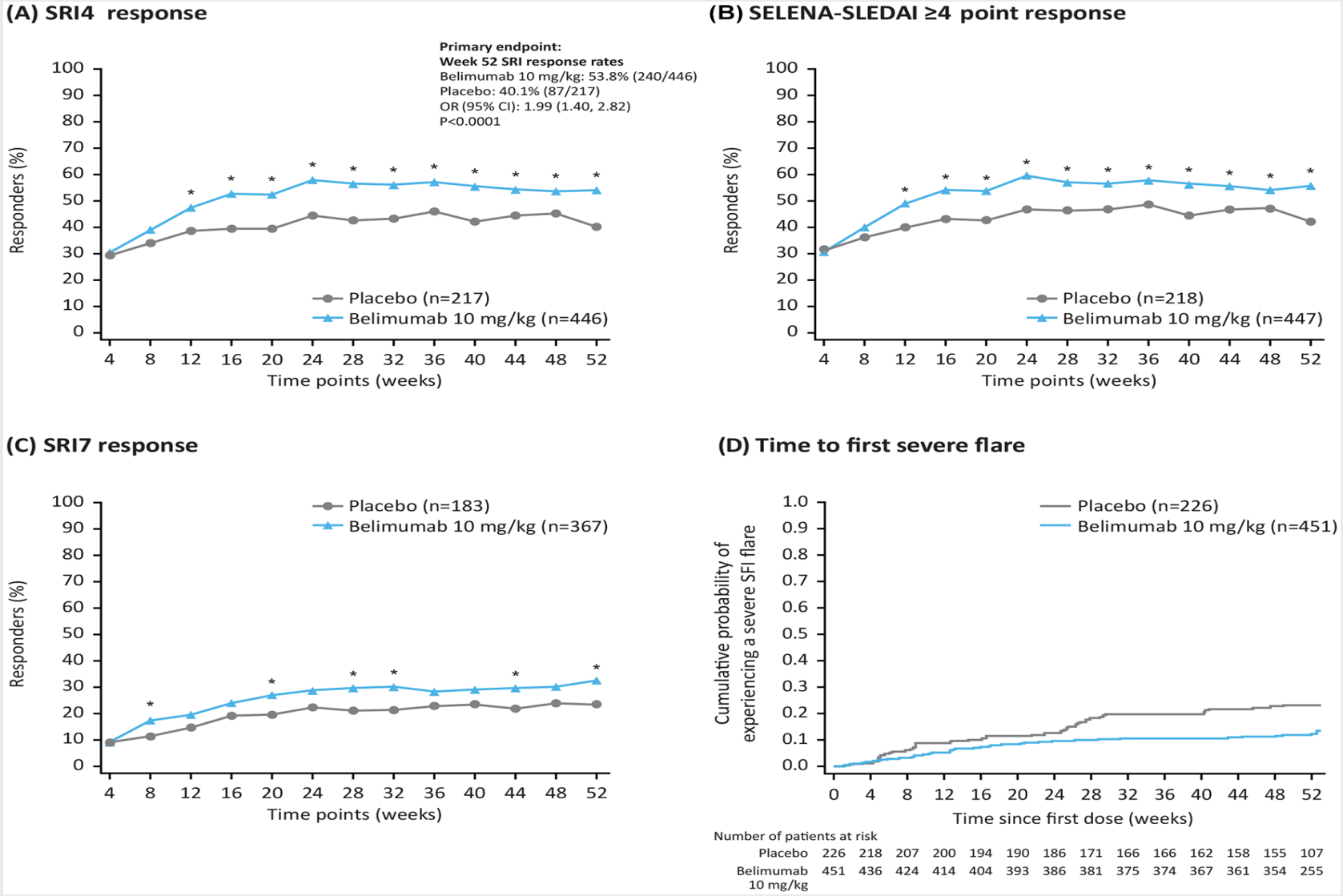
BLISS-76: SLE Responder Index: % Response at Week 52

Week 76 response rates of Belimumab groups were not significantly different from placebo - the secondary endpoint was not met

The responder index used in the BLISS studies was built around SLEDAI

Belimumab was generally well-tolerated in both studies

UPDATE ON BENLYSTA (2)



Zhang F et al. Ann Rheum Dis 2018; 77: 355-363

UPDATE ON BENLYSTA (3)

1. **Approved by the FDA (2011) for use in SLE patients with skin and joint disease.**

2. **Approved by NICE (2016) under stringent conditions with a pending review after 300 patients are treated.**

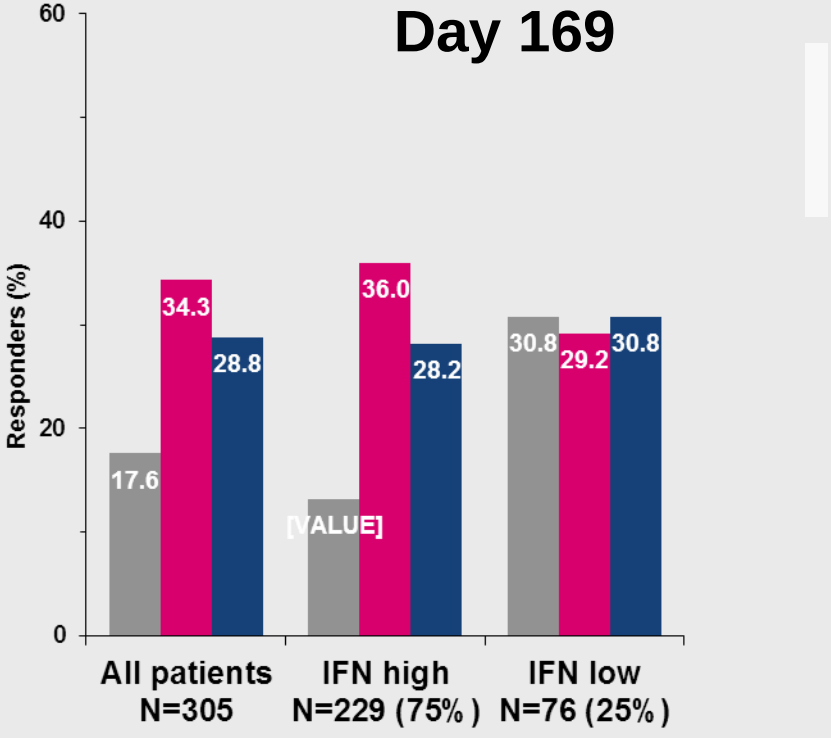
3. **Long-term studies confirm this is a safe drug with benefit in approximately 2/3 of patients.**

OVERVIEW – BIOLOGIC TREATMENT IN LUPUS -3-

BIOLOGIC	TRIAL RESULTS	CURRENT 'REAL WORLD USE'
BLOCKING INTERFERON α **Sifalimumab**	**Primary endpoint (SR1-4 at 1 year) was achieved in a phase III study.**	**No further studies.**
Anifrolumab	**Primary endpoint (SR1-4 at 1 year) was achieved in a phase III study.**	**Further studies ongoing .**
Rontalizumab	**ROSE - FAILED** **(Some improvement in disease activity and ↓ steroid use in those with low interferon signature gene expression).**	**Genentech will not undertake any further studies.**

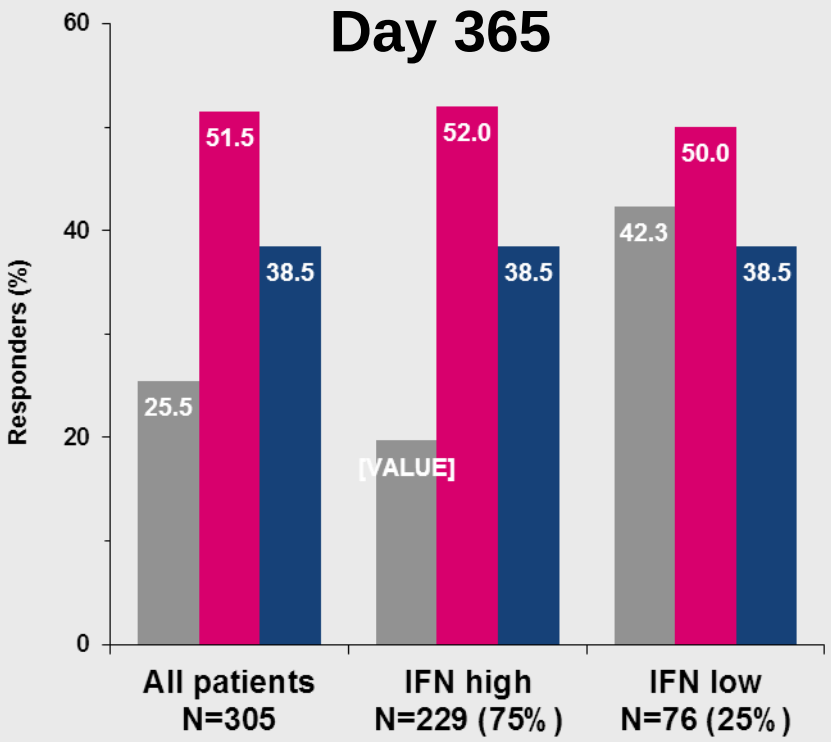
SRI(4) INCLUDING OCS TAPER

Primary endpoint
Day 169



	300 mg	1,000 mg	300 mg	1,000 mg	300 mg	1,000 mg
Delta:	16.7%	11.2%	22.8%	15.0%	-1.6%	0.0%
OR:	2.38	1.94	3.55	2.65	0.96	1.04
90% CI:	(1.33, 4.26)	(1.08, 3.49)	(1.72, 7.32)	(1.27, 5.53)	(0.34, 2.74)	(0.37, 2.88)
P:	0.014	0.063	0.004	0.029	0.946	0.953

Secondary endpoint
Day 365



300 mg	1,000 mg	300 mg	1,000 mg	300 mg	1,000 mg
26.0%	13.0%	32.3%	18.8%	7.7%	-3.8%
3.08	1.84	4.30	2.52	1.47	0.89
(1.86, 5.09)	(1.11, 3.04)	(2.34, 7.91)	(1.37, 4.64)	(0.55, 3.93)	(0.34, 2.35)
<0.001	0.048	<0.001	0.013	0.514	0.849

Placebo Anifrolumab 300 mg Q4W Anifrolumab 1,000 mg Q4W

Dropouts and patients whose medication use exceeded protocol threshold were imputed as failures.

Delta=dosage vs. placebo .

BUT SADLY….

- **On 31 August AstraZeneca/MedImmune announced:**

“The phase lll TULIP 1 trial (a randomized double-blind 52-week placebo-controlled multi-centre trial of Anifrolumab in adult patients with moderate-to-severe SLE) did not meet the primary end point as measured by the SRI4 index.”

We await results of the TULIP 2 trial later this year.

AND AFTER BENLYSTA/RITUXIMAB/? ANIFROLUMAB

Possibilities being investigated:-

1. **Fully humanised anti-CD20 monoclonals**
2. **Blocking BAFF and APRIL (Atacicept)**
3. **Anti-CD40 L (Dapirolizumab)**
4. **Antibodies to FcγIIB (SM 101)**
5. **BTK covalent small molecule inhibitor (Ibrutinib)**
6. **P140 peptide (Lupuzor) blocks auto reactive T cells**

NOT ONLY ….BUT ALSO….

1. Anti-Il-12/23 (Ustekinumab)
2. Anti-Il-3R (CD23)
3. JAK-STAT inhibition (Baricitinib)
4. Anti-Bcl 2 antagonist (Venetoclax)
5. Small peptide influencing T-cell function based on the 16/6/ DNA antibody idiotype
6. Low-dose Interleukin-2 (He et al. Nature Med 2016; 22: 991

THE ELEPHANT IN THE ROOM

THE ISSUE OF COMPLIANCE!

COMPLIANCE ISSUES – HYDROXYCHLOROQUINE LEVELS IN SLE PATIENTS (1)

CENTRE	Patient Number	Visit Date	Hydroxychloroquine measurements ng/ml
013	013-001-S-R	29/04/2013	319
013	013-002-C-P	03/06/2013	1747
013	013-003-I-P	03/06/2013	0
013	013-004-E-M	03/06/2013	370
013	013-005-A-O	05/06/2013	107
013	013-006-A-C	10/06/2013	792
013	013-007-O-A	17/06/2013	186
013	013-008-S-S	17/06/2013	146
013	013-009-H-J	04/07/2013	1721
013	013-010-P-R	15/07/2013	595
013	013-011-C-R	22/07/2013	1770
013	013-012-G-B	19/08/2013	1151
013	013-013-S-N	02/09/2013	1227
013	013-014-G-C	16/09/2013	1262
013	013-015-T-R	23/09/2013	30
013	013-016-B-J	23/09/2013	1457
013	013-017-B-C	25/11/2013	58
013	013-018-B-C	16/12/2013	1699
013	013-019-L-N	06/01/2014	1032
013	013-020-O-C	13/01/2014	987
013	013-021-F-I	20/01/2014	874
013	013-022-Y-T	03/02/2014	423
013	013-023-D-A	24/02/2014	0
013	013-024-N-D	10/03/2014	732
013	013-025-W-C	17/03/2014	723
013	013-026-M-C	24/03/2014	820
013	013-027-J-D	31/03/2014	0

Courtesy of Prof Nathalie Costedoat-Chalumeau

COMPLIANCE ISSUES – HYDROXYCHLOROQUINE LEVELS IN SLE PATIENTS (2)

013	013-028-R-R	07/04/2014	469
013	013-029-F-M	28/04/2014	951
013	013-030-A-M	19/05/2014	0
013	013-031-E-A	16/06/2014	1331
013	013-032-P-V	16/06/2014	905
013	013-033-L-E	16/06/2014	1279
013	013-034-R-J	23/06/2014	525
013	013-035-C-D	14/07/2014	1969
013	013-036-C-J	04/08/2014	2019
013	013-037-V-C	11/08/2014	2790
013	013-038-K-R	11/08/2014	175
013	013-039-P-D	08/09/2014	235
013	013-040-P-L	06/10/2014	725
013	013-041-G-G	13/10/2014	1060
013	013-042-P-A	20/10/2014	172
013	013-043-K-N	03/11/2014	130
013	013-044-P-S	24/11/2014	1928
013	013-045-D-A	26/01/2015	0
013	013-047-H-M	09/02/2015	1351
013	013-048-T-A	09/02/2015	1497
013	013-049-T-R	16/02/2015	0
013	013-050-W-G	23/02/2015	549
013	013-051-A-M	30/03/2015	0
013	013-052-C-R	13/04/2015	116
013	013-053-J-A	20/04/2015	1548
013	013-054-A-S	01/06/2015	265
013	013-055-K-W	08/06/2015	1339
013	013-056-J-V	15/06/2015	127

CONCLUSIONS (1)

1. **The mortality from SLE has improved significantly in the past 50 years.**
2. **We are moving from an era of "serendipity to sense" introducing new therapies on a far more rational basis.**
3. **Unfortunately the successful use of biologic drugs in SLE lags behind that for RA and psoriatic arthritis (by about a decade!)**
4. **Early open-label success with Rituximab was not followed by clinical trials which met their endpoints with either this drug or several others (although it is widely acknowledged that Rituximab does work for many patients).**

CONCLUSIONS (2)

5. Benlysta (anti-BAFF) met its clinical trial endpoints and is approved by the FDA and (belatedly) NICE.

6. Very encouraging results are now emerging with the use of Atacicept (anti-BAFF and APRIL) and blocking interferon-alpha (especially in those with high signature)

7. We await more, successful trials of biological therapies for SLE.

8. More careful thought needs to be given to the design of clinical trials.

9. The first use of combinations of biologics in SLE is underway.

10. The use of biological therapy in lupus patients at diagnosis needs to be formally tested.

UPDATE ON SLE TREATMENT – THE DENOUEMENT!

PAST IMPERFECT

FUTURE TENSE

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