Terapias biológicas en el LES

Dr. Luis Sáez C
Unidad Enfermedades Autoinm
Sistér
Servicio de Medicina In
Hospital Universitario Miguel S
Zara

CONFLICTOS DE INTERÉS

Speaking fees from GlaxoSmithKline

Capilaroscopy courses for Acthelion

Participated in BIOGEAS, RESCLE, RELES,

REVAS, REGAS, DUO registry

Participating in anti-TWEAK trial

BIOLÓGICOS EN LES:

1.Qué biológicos podemos utilizar en LES? Cuándo?

2.Son seguros?

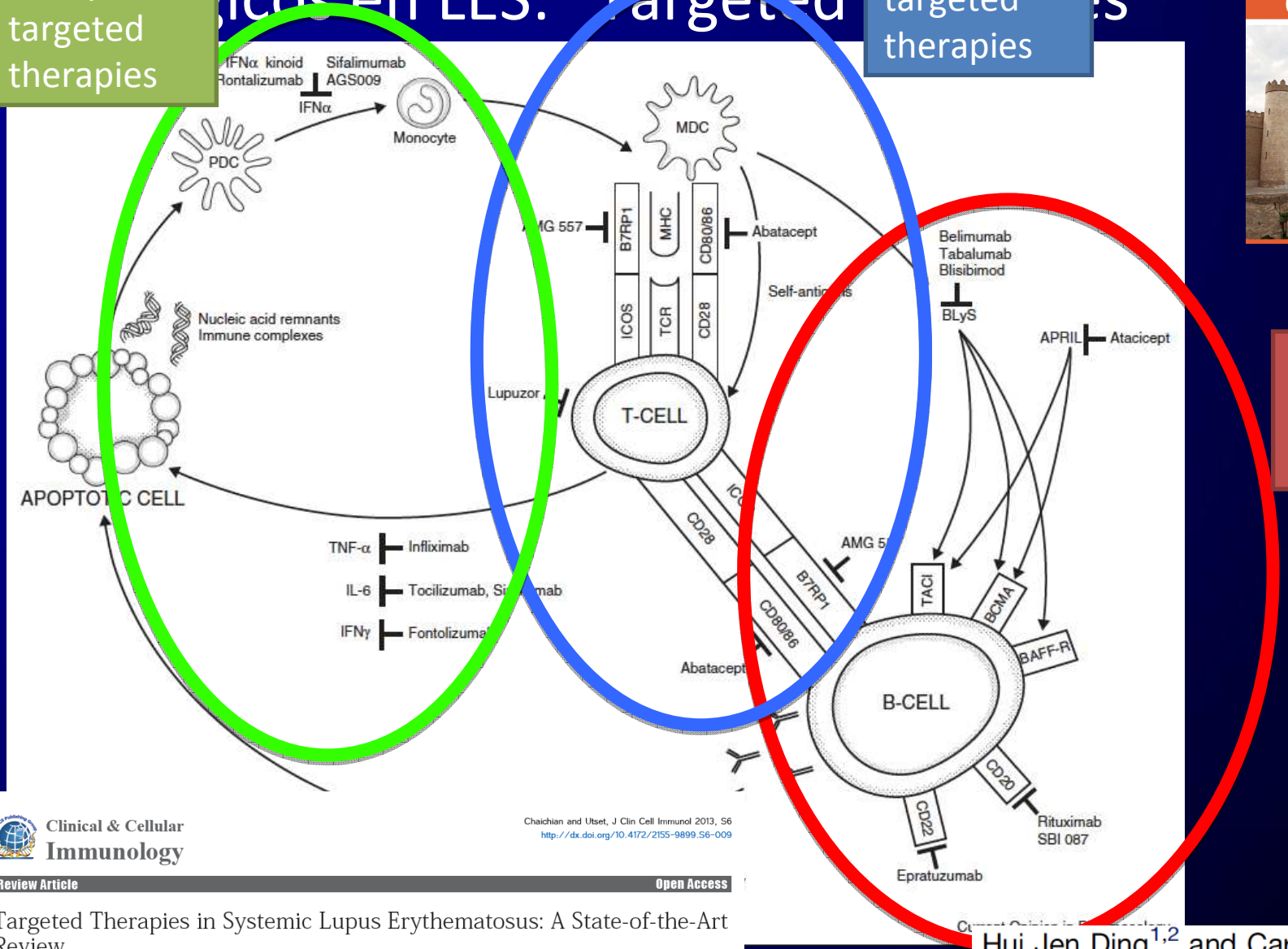
3.Son caros?

4.Futuro: Cuál es el biológico ideal? Cuál será el próximo?

Anti-citokyne targeted therapies

sicos en LES: "Targeted es"

T-cell targeted therapies



B-cell targeted therapies

Clinical & Cellular Immunology

Chaichian and Utset, J Clin Cell Immunol 2013, S6
http://dx.doi.org/10.4172/2155-9899.S6-009

Review Article Open Access

Targeted Therapies in Systemic Lupus Erythematosus: A State-of-the-Art Review

Yashaar Chaichian and Tammy O. Utset*
Section of Rheumatology, University of Chicago, Chicago, IL 60637, USA

Hui Jen Ding[1,2] and Caroline Gordon[1,3]

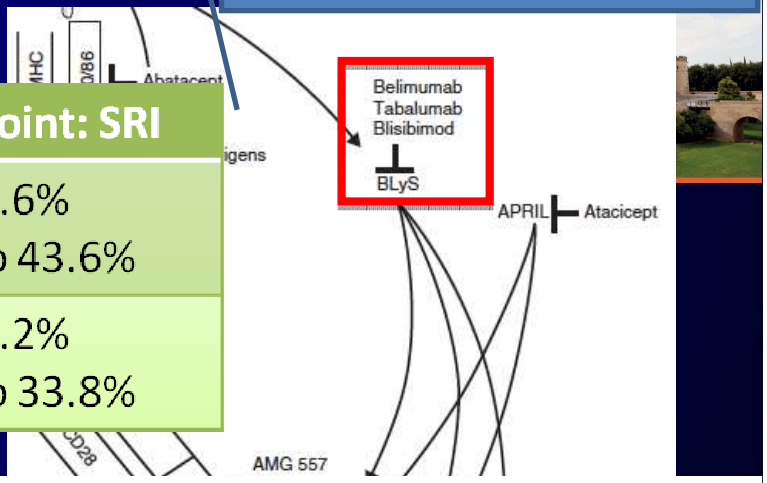
Current Opinion in Pharmacology 2013, **13**:405–412

Qué biológicos están indicados en LE

BELIMUMAB (⇥ BLyS)

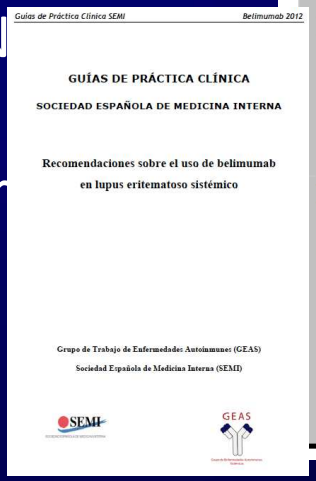
>=4pts reduction SLEDAI
No new BILAG A
No worsening PGA

Trial	n	Dose	Endpoint: SRI
BLISS-52	865	SOC ± BLM 10 mg/kg IV 0,2,4w → /mo 52w	BLM 57.6% placebo 43.6%
BLISS-76	826	SOC ± BLM 10 mg/kg IV 0,2,4w → /mo 76w	BLM 43.2% placebo 33.8%



Pacientes "BLISS":

- "Activos": SLEDAI > 6? 10?
- Seropositivos: AN
(C bajo)
- Cutáneo-articular
- No renal, no SNC


Guías de Práctica Clínica SEMI — Belimumab 2012

GUÍAS DE PRÁCTICA CLÍNICA

SOCIEDAD ESPAÑOLA DE MEDICINA INTERNA

Recomendaciones sobre el uso de belimumab en lupus eritematoso sistémico

Grupo de Trabajo de Enfermedades Autoinmunes (GEAS)
Sociedad Española de Medicina Interna (SEMI)

SEMI GEAS

Tabla 3. Perfil general del paciente con LES candidato a tratamiento con belimumab

Perfil	Definición
Edad	> 18 años
Perfil inmunológico	ANA ≥1:80 y/o anti-DNAn ≥30 IU/mL : - en dos ocasiones previas - al menos un marcador positivo al tratamiento - especial atención si además hipocomplementemia
Nivel de actividad	Puntuación mínima SELENA-SLEDAI de 6
Tratamiento	No respuesta a tratamiento estándar - Necesidad diaria de corticoides 7.5-15 mg/d y - Antipalúdico y - Inmunodepresor oral Intolerancia a tratamiento estándar

Qué biológicos están indicados en LES?

RITUXIMAB (↛ CD20)

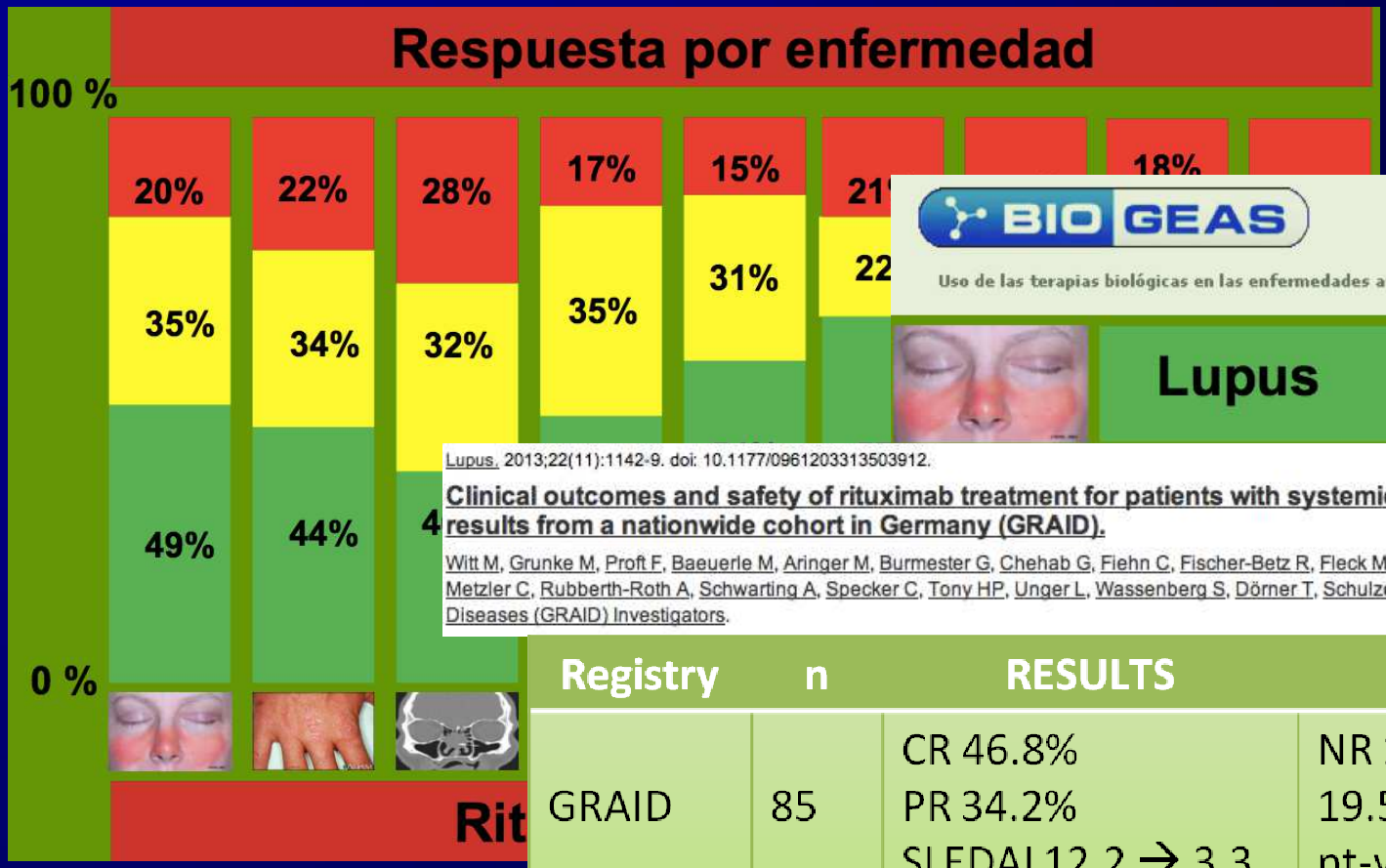
Efficacy and safety of rituximab therapy for systemic lupus erythematosus: a systematic review and meta-analysis

Observational (n)	Patients	F-up	% response
611	85% ♀ Age 33.6y 36.3% LN 94.3% refractory or relapse with immn-	18mo	BCD in 80.6% (12w → 12-48mo) Remission in 460 (58.5%): • 116 partial (25.2%) • 153 complete (33.3%) 80.2%: reduce in SLEDAI
	220 LN (116 assessing response)		34.5% PR (37.6% in LN IV) 37.9% CR (39.6% in LN IV)

RCT (2)	n/control	Patients	Dose	F-up	% response
EXPLORER	169/88	Mod-severe active extra-renal SLE	AZA/MMF/MTX + PRED ± 2x1g/15d → rept 6mo	56w	No diffs RTX vs placebo (major clin response, BILAG, TTF, QoL)
LUNAR	72/72	Class III/IV active LN	MMF 3g/d + PRED+HCQ ± 2x1g/15d → rept 6mo	52w	No diffs RTX vs placebo (CR, PR, C3, C4)

Qué biológicos están indicados en LES?

RITUXIMAB (↛ CD20): registros



BIO GEAS

Uso de las terapias biológicas en las enfermedades autoinmunes sistémicas

Lupus 162 (42 %)

Lupus. 2013;22(11):1142-9. doi: 10.1177/0961203313503912.

Clinical outcomes and safety of rituximab treatment for patients with systemic lupus erythematosus (SLE) - results from a nationwide cohort in Germany (GRAID).

Witt M, Grunke M, Proft F, Baeuerle M, Aringer M, Burmester G, Chehab G, Fiehn C, Fischer-Betz R, Fleck M, Freivogel K, Haubitz M, Kötter I, Lovric S, Metzler C, Rubberth-Roth A, Schwarting A, Specker C, Tony HP, Unger L, Wassenberg S, Dörner T, Schulze-Koops H; German Registry of Autoimmune Diseases (GRAID) Investigators.

Registry	n	RESULTS	AEs
GRAID	85	CR 46.8% PR 34.2% SLEDAI 12.2 → 3.3	NR 19% 19.5 infecciones/100 pt-y (6 graves)

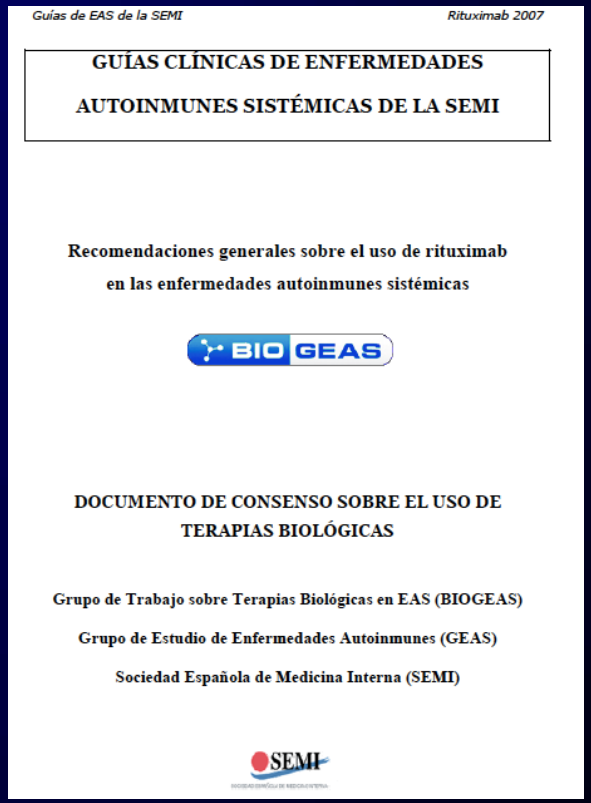
Qué biológicos están indicados en LES?

RITUXIMAB (↛ CD20): indicaciones

Casos graves refractarios/intolerancia a tto convencional → USO FUERA INDICACIÓN

Se aconseja:

- Criterios clasificación (o riesgo vital o claro proceso autoinmune de base)
- Descartar infección
- NO resp adecuada al tto x:
  - Falta resp a SOC (inducción/mantº): pred >0.5 mg/kg/d >3m o fracaso en ≥ 2 immn-
  - Intolerancia o EA a corticoides/immn-



Guías de EAS de la SEMI *Rituximab 2007*

GUÍAS CLÍNICAS DE ENFERMEDADES AUTOINMUNES SISTÉMICAS DE LA SEMI

Recomendaciones generales sobre el uso de rituximab en las enfermedades autoinmunes sistémicas

BIO GEAS

DOCUMENTO DE CONSENSO SOBRE EL USO DE TERAPIAS BIOLÓGICAS

Grupo de Trabajo sobre Terapias Biológicas en EAS (BIOGEAS)

Grupo de Estudio de Enfermedades Autoinmunes (GEAS)

Sociedad Española de Medicina Interna (SEMI)

SEMI

Qué biológicos están indicados en LES?

RITUXIMAB (↛ CD20): consensos

Terapias biológicas en el lupus eritematoso sistémico

Actualmente, el BLM es la única TB con indicación aprobada en LES, aunque se han utilizado fuera de indicación el rituximab, tocilizumab, abatacept (ABT) y los inhibidores del TNF-α.

Reumatol Clin. 2013;9(5):281–296

ELSEVIER DOYMA

Reumatología Clínica

www.reumatologiaclinica.org

Original

Consenso de la Sociedad Española de Reumatología sobre el uso de terapias biológicas en el lupus eritematoso sistémico

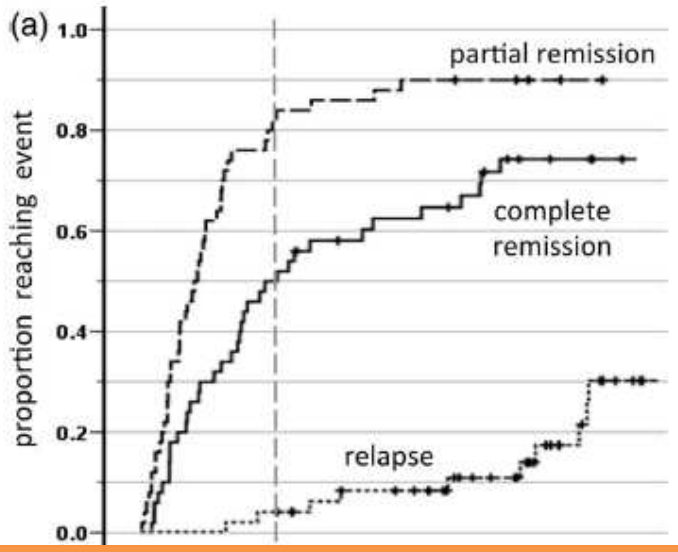
Jaime Calvo-Alén[a], Lucía Silva-Fernández[b,*], Eduardo Úcar-Angulo[c], José María Pego-Reigosa[d], Alejandro Olivé[e], Carmen Martínez-Fernández[f], Víctor Martínez-Taboada[g], José Luis Marenco[h], Estíbaliz Loza[i], Javier López-Longo[j], Juan Jesús Gómez-Reino[k], María Galindo-Izquierdo[l], Antonio Fernández-Nebro[m], María José Cuadrado[n], María Ángeles Aguirre-Zamorano[o], Antonio Zea-Mendoza[p] e Íñigo Rúa-Figueroa[q]

Clinical and epidemiological research

EXTENDED REPORT

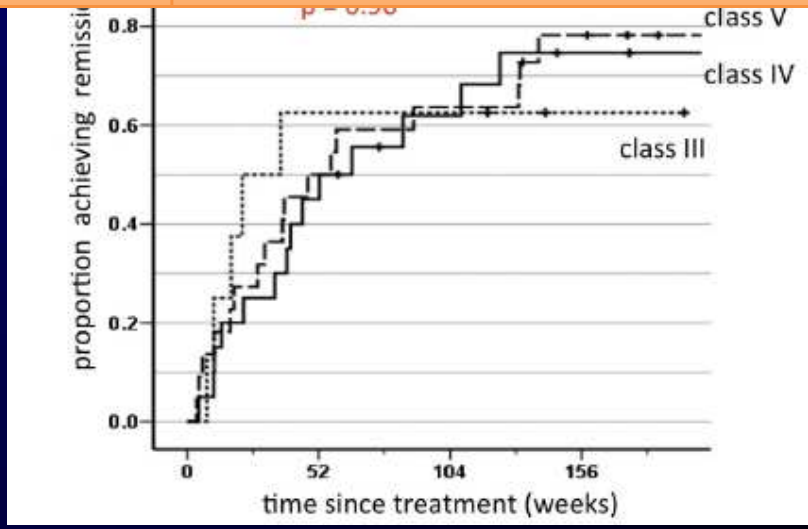
Prospective observational single-centre cohort study to evaluate the effectiveness of treating lupus nephritis with rituximab and mycophenolate mofetil but no oral steroids

Marie B Condon,[1] Damien Ashby,[1] Ruth J Pepper,[1] H Terence Cook,[1,2] Jeremy B Levy,[1] Megan Griffith,[1] Tom D Cairns,[1] Liz Lightstone[1,2,3]



"Rituxi-lupus", "steroid-free"

n	Tx protocol	RESULTS	AEs
50 LN III, IV or V	1000 RTX + 500 MPIV days 1 & 15 MMF	45/50 (90%) CR or PR: 72% CR 36w 18% PR 32w	12 relapses (65w) 6 systemic flares 18% admissions (10% infections)

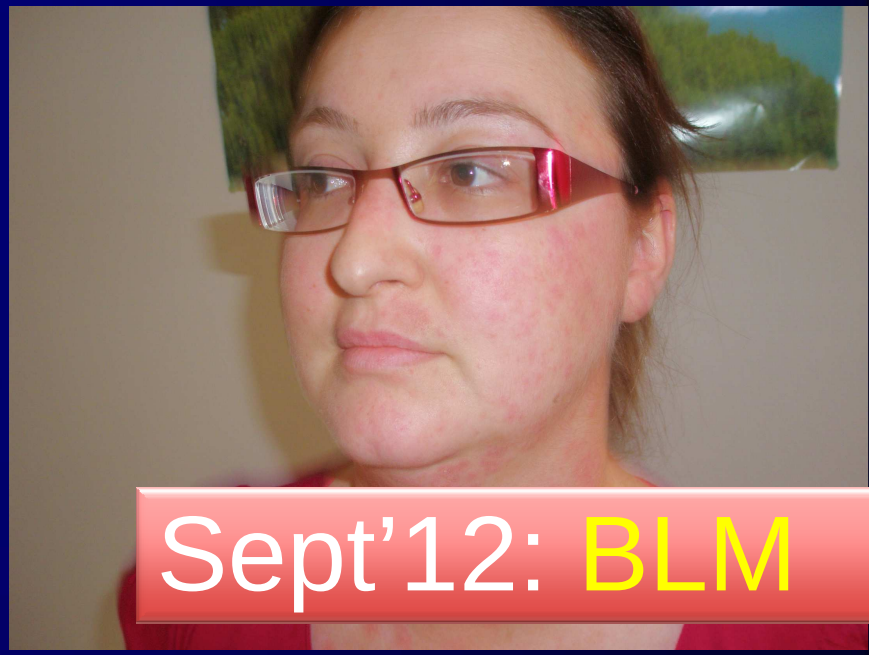


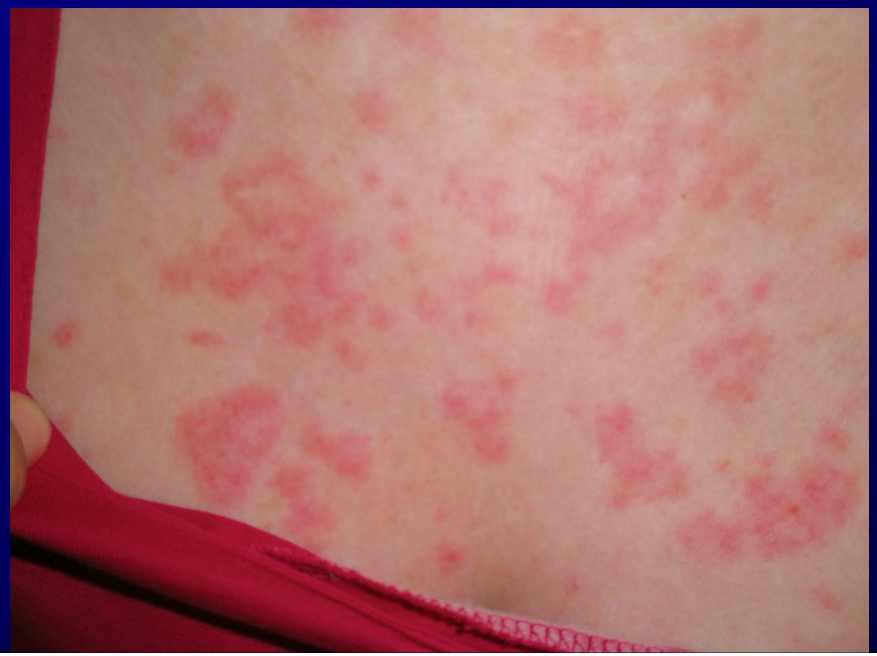
Jul'12

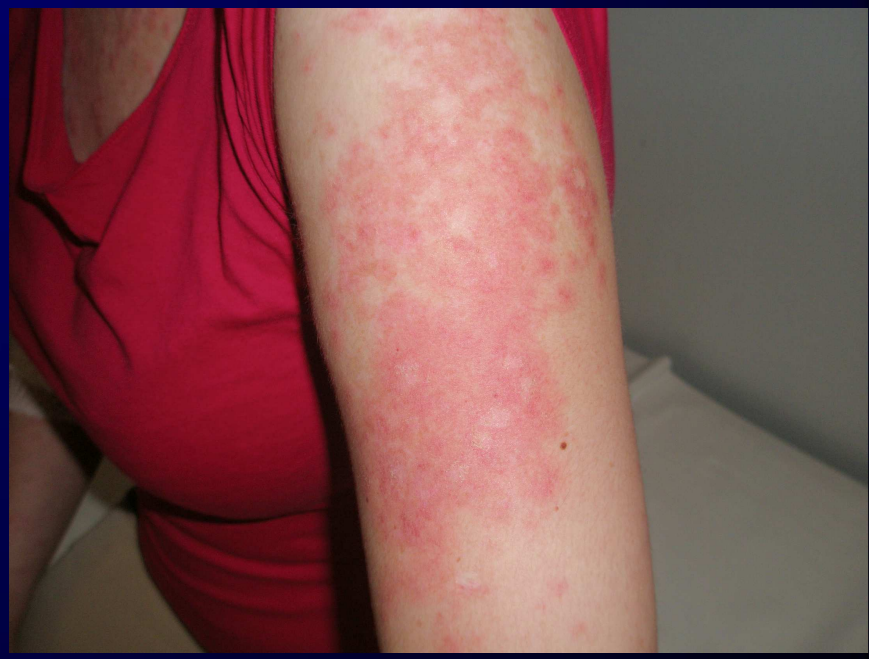
31ª
LES cutáneo-articular
ANA+, RO+, DNA+

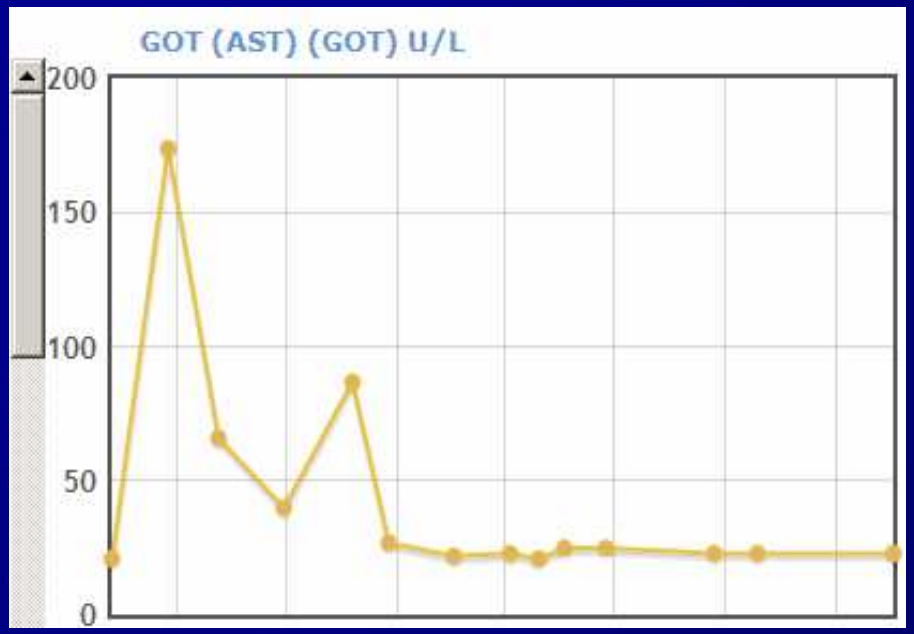
TTOS PREVIOS:

~~Cloroquina~~
Isotretinoina
Azatioprina
Corticoides orales y tópicos: 15-30 mg/d
Tacrolimus tópico y oral
Micofenolato mofetilo
Ciclosporina
~~MTX~~

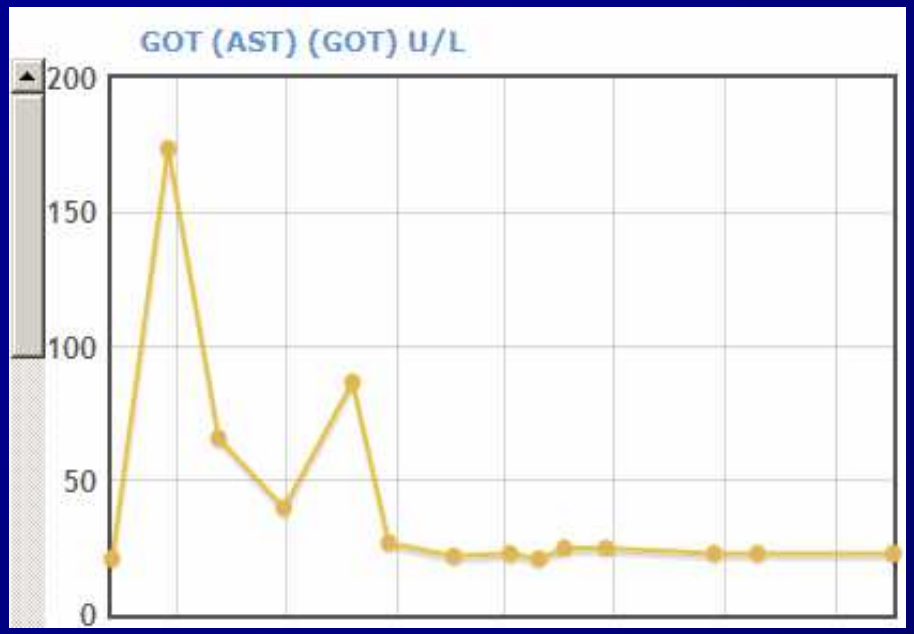




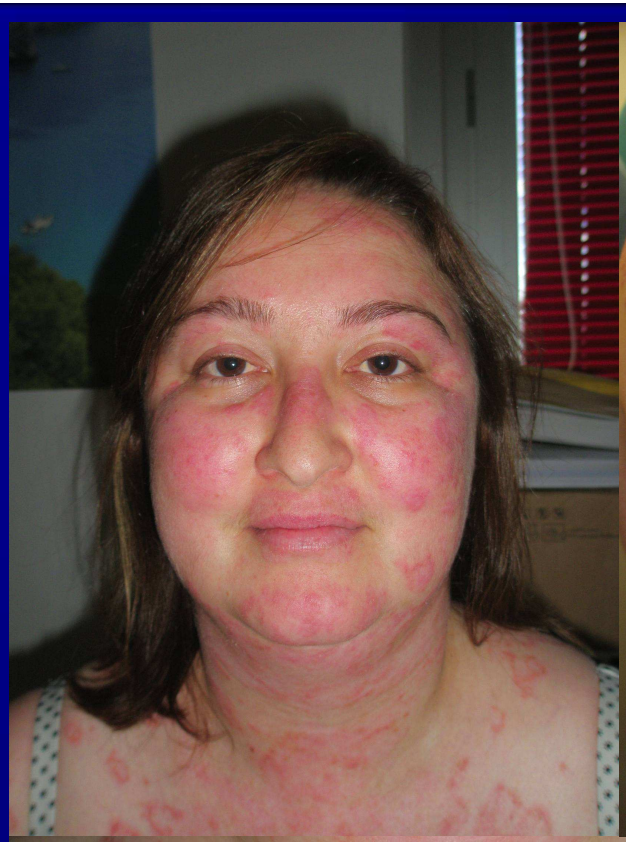


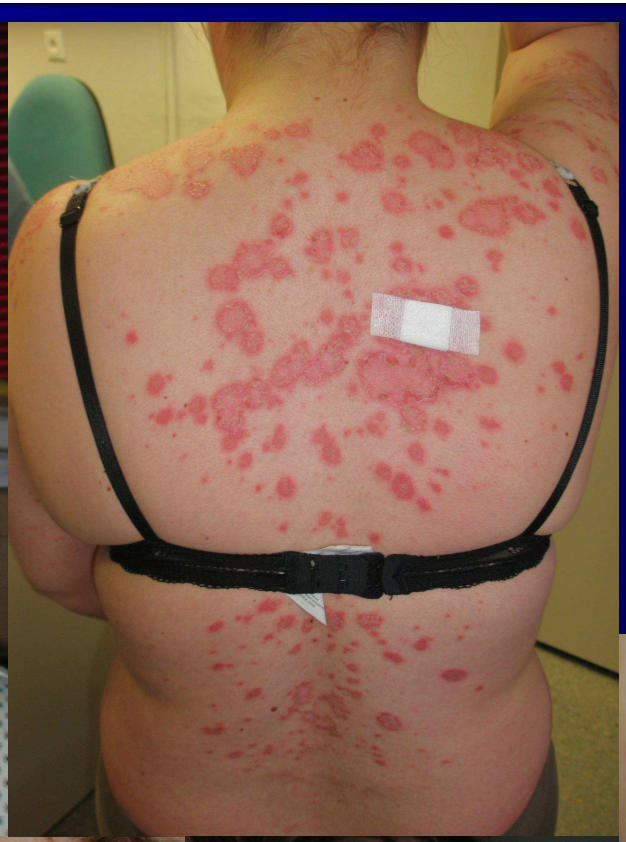


BLM 0, 14, 28d → mensual



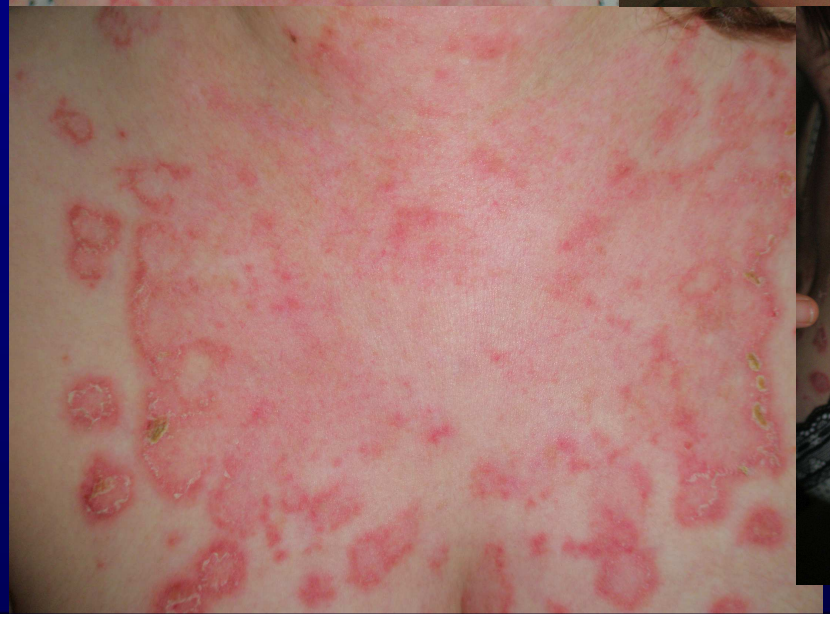
BLM 0, 14, ~~28d → mensual~~

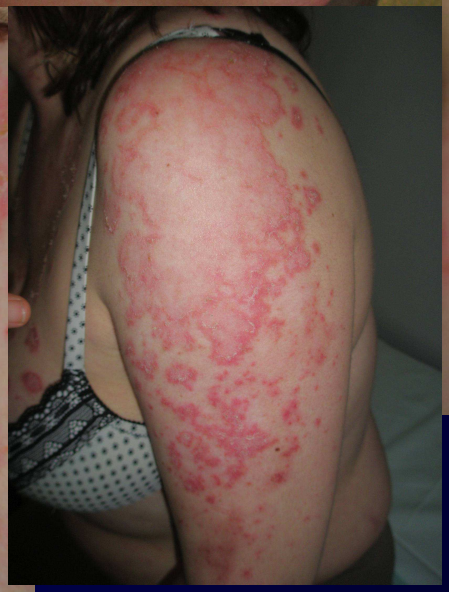


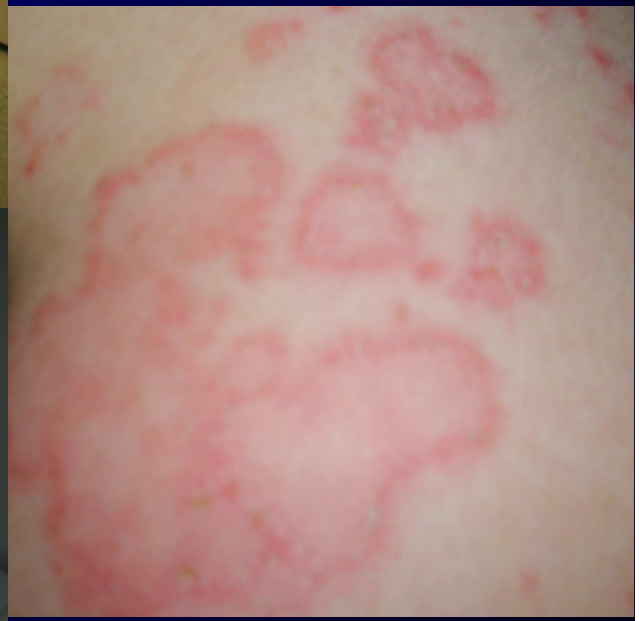


Mar’13

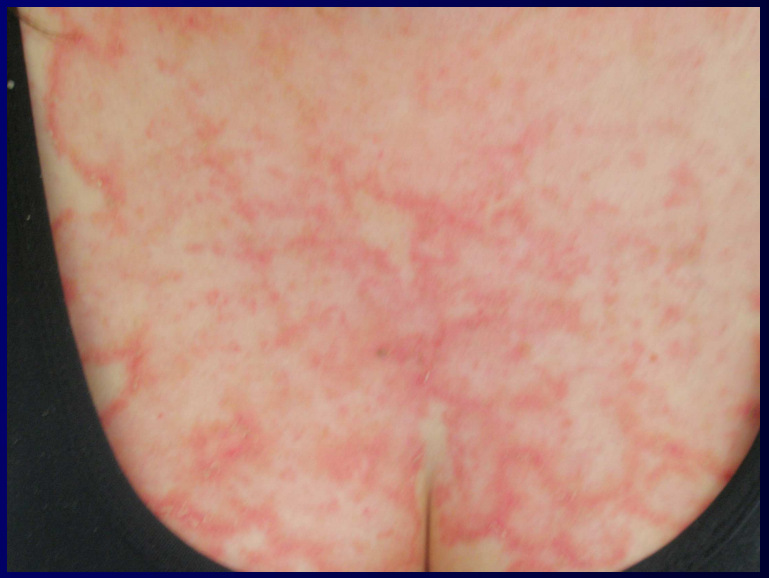
<u>TTOS:</u>
Corticoides
MMF
Mepacrina

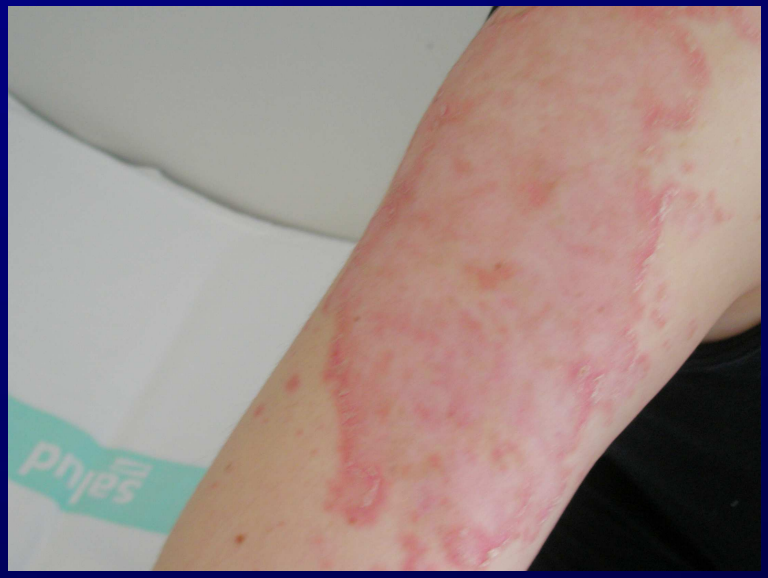


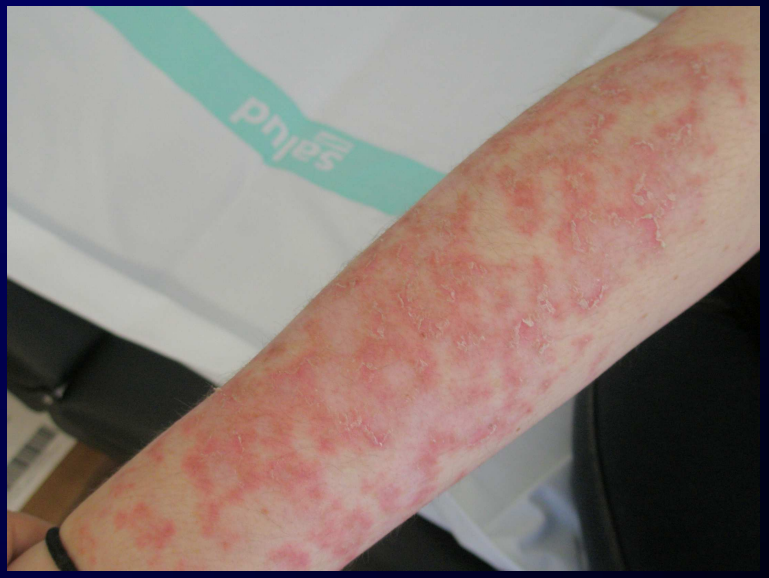




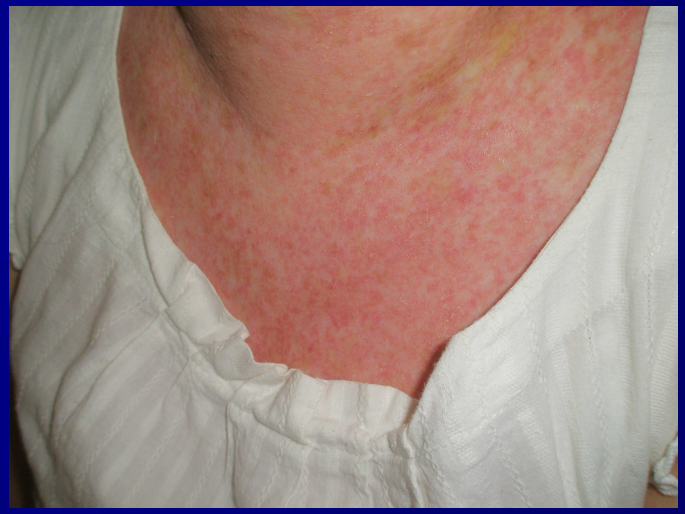
Abr'13: RTX

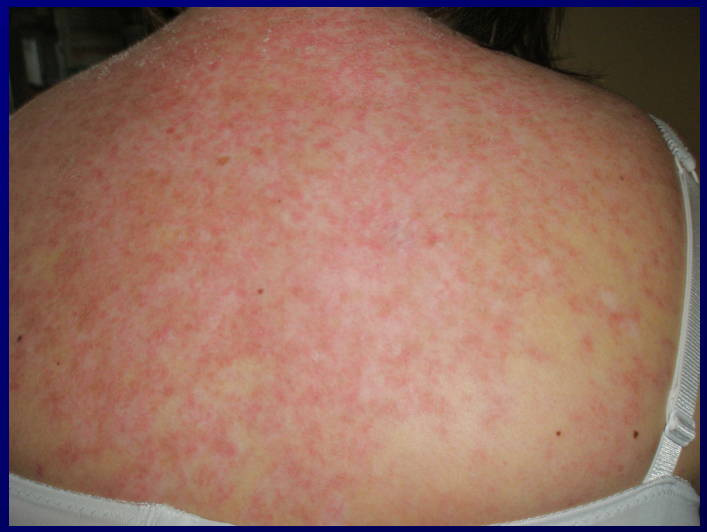


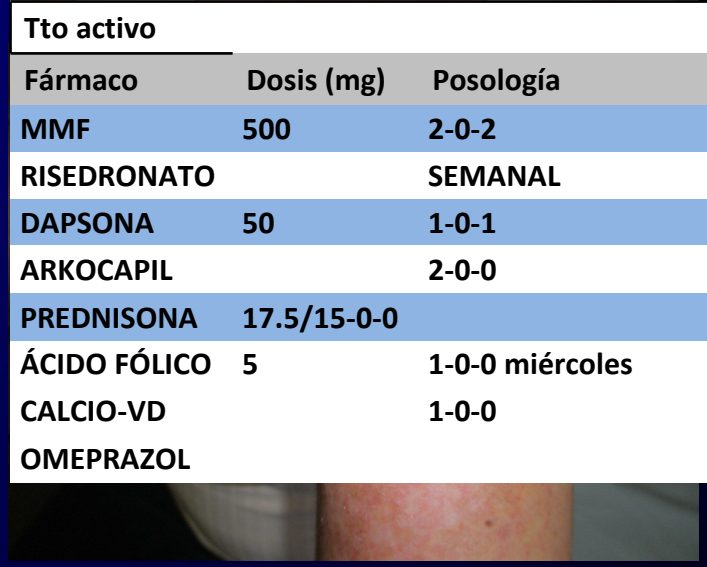




Oct'13: RTX? IGIV?







Tto activo

Fármaco	Dosis (mg)	Posología
MMF	500	2-0-2
RISEDRONATO		SEMANAL
DAPSONA	50	1-0-1
ARKOCAPIL		2-0-0
PREDNISONA	17.5/15-0-0	
ÁCIDO FÓLICO	5	1-0-0 miércoles
CALCIO-VD		1-0-0
OMEPRAZOL		

Otros “B-cell-targeted therapies” en LES

VI Reunión GEAS
17 y 18 de Octubre de 2013

B-cell targeted

Target	Agent	Mechanism of Action	Key Clinical Trials (*denotes ongoing or upcoming trial)	Primary Endpoint Met
B cells	Rituximab	Chimeric monoclonal anti-CD20 antibody	Phase III (EXPLORER) [67]: SLE	No
			Phase III (LUNAR) [68]: lupus nephritis	No
			Phase III (RING) [69]*: lupus nephritis	
B cells	Belimumab	BLyS inhibitor	Phase III (BLISS 52) [70]: SLE	Yes
			Phase III (BLISS 76) [71]: SLE	Yes (only for 10 mg/kg Belimumab group)
			Phase III (BLISS-LN) [73]*: lupus nephritis	
			Phase III/IV (EMBRACE) [75]*: SLE in African Americans	
B cells	Atacicept	BLyS and APRIL inhibitor	Phase II/III (APRIL-LN) [79]: lupus nephritis	No (study prematurely terminated)
			Phase II/III [80] (APRIL SLE)*: SLE	
B cells	Abetimus	B cell tolerogenic DNA-oligomeric construct active against anti-dsDNA	Phase II/III [82]: lupus nephritis	No
			Phase III [83]: lupus nephritis	No
B cells	Ocrelizumab	Humanized monoclonal anti-CD20 antibody	Phase III (BEGIN) [84]: SLE	No (study prematurely terminated)
			Phase III (BELONG) [85]*: lupus nephritis	
B cells	Epratuzumab	Humanized monoclonal anti-CD22 antibody	Phase II (EMBLEM) [87]: SLE	Yes
			Phase III (EMBODY 1) [88]*: SLE	

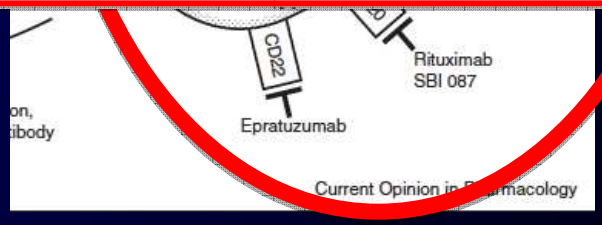
Clinical & Cellular Immunology

Chaichian and Utset, J Clin Cell Immunol 2013, S6
http://dx.doi.org/10.4172/2155-9899.S6-009

Review Article Open Access

Targeted Therapies in Systemic Lupus Erythematosus: A State-of-the-Art Review

Yashaar Chaichian and Tammy O. Utset*
Section of Rheumatology, University of Chicago, Chicago, IL 60637, USA



"B-cell targeted therapies" en LES

EPRATUZUMAB (⇥ CD22, Partial depletion B-cells, Alt migration)

Trials, year	Phase	SLE pts	Patients	F-up	% response
Dörner et al, 2006	I	Moderately active	14		Improved clinical and biochemically
ALLEVIATE	II	Moderate/severe active non-renal			Reduction in BILAG, CS, accept safety profile Discontinued due to interruption in drug supply
EMBLEM	IIb	Moderate/severe	227 (38 placebo vs dif dosing EPT)	12w	2400 mg clin effective 600 mg improves BILAG
EMBODY 1	III	Moderate/sev	780	48w	Recruiting

Otros “B-cell-targeted therapies” en LES

Anti-CD20:

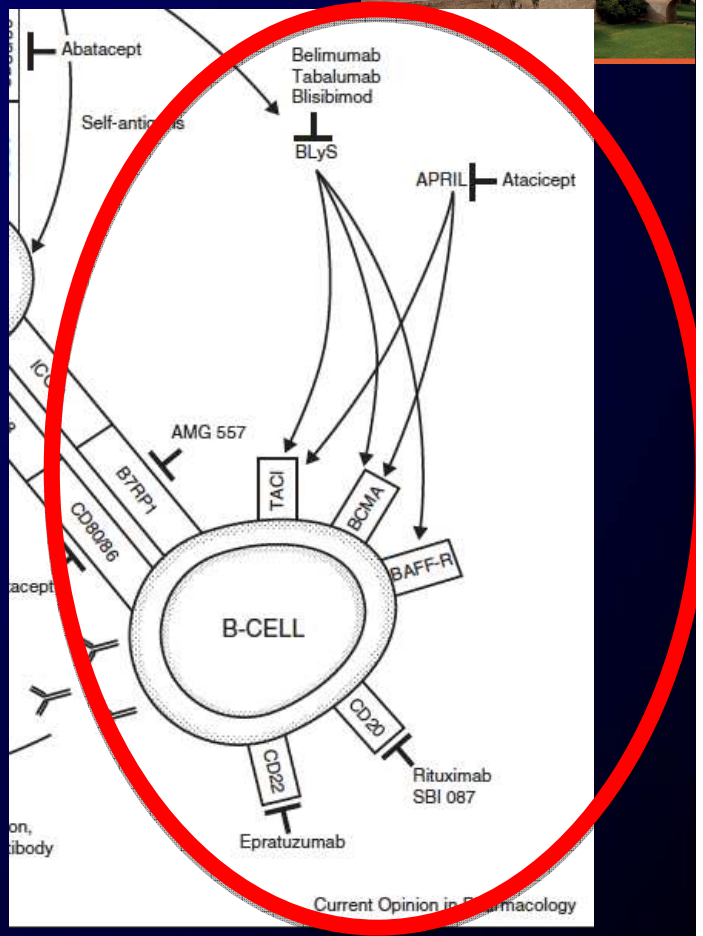
•Ocrelizumab, stopped x IOs

Anti-BLys:

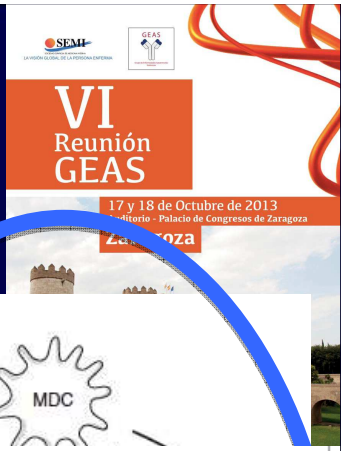
•Tabalumab (sc)

•Blisibimod → PEARL-SC (II) , CHABLIS-SC 1&2 (III, 2012)

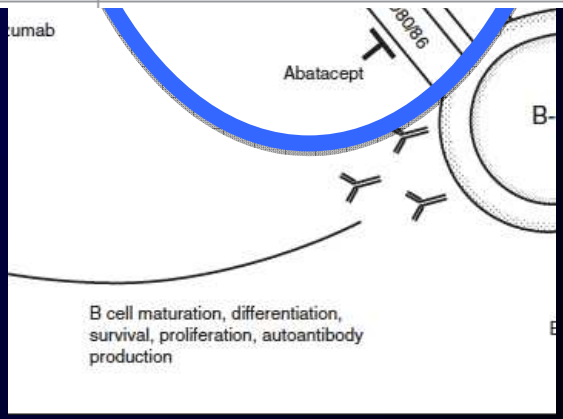
Atacicept (anti-BLys, anti-APRIL) stopped x low IGG



“T-cell targeted therapies” en LES



T cells	Abatacept	T-cell costimulation blockade	Phase IIb [89]: SLE Phase II/III [90]: lupus nephritis Phase II (ACCESS), Phase III [91,92]*: lupus nephritis	No No (study prematurely terminated)
T cells	Rapamycin	Regulation of mitochondrial transmembrane potential and calcium flow	Phase I [93]: SLE Phase II [94]*: SLE	Preliminary efficacy observed
T cells	N-acetylcysteine	mTOR inhibitor in T lymphocytes	Phase I/II [95]: SLE	Preliminary efficacy observed (except for 1.2 g daily N-acetylcysteine group)
T cells	R788	Spleen tyrosine kinase inhibitor	None (only murine lupus data) [96,97]	
T cells	BG9588	Humanized anti-CD40 ligand antibody	Phase II [99]: SLE	No (study prematurely terminated)
T cells	Laquinimod	Promotes TH2 over TH1 response	Phase IIa [101]*: SLE Phase IIa [102]*: lupus nephritis	
T cells	Paquinimod	Promotes TH2 over TH1 response	Phase Ib [103]: SLE	N/A



ARD Online First, published on November 21, 2012 as 10.1136/annrheumdis-2012-202460
Clinical and epidemiological research

OPEN ACCESS

EXTENDED REPORT

Lupuzor/P140 peptide in patients with systemic lupus erythematosus: a randomised, double-blind, placebo-controlled phase IIb clinical trial

Robert Zimmer,[1] Hugo R Scherbarth,[2] Oscar Luis Rillo,[3] Juan Jesus Gomez-Reino,[4] Sylviane Muller[5]

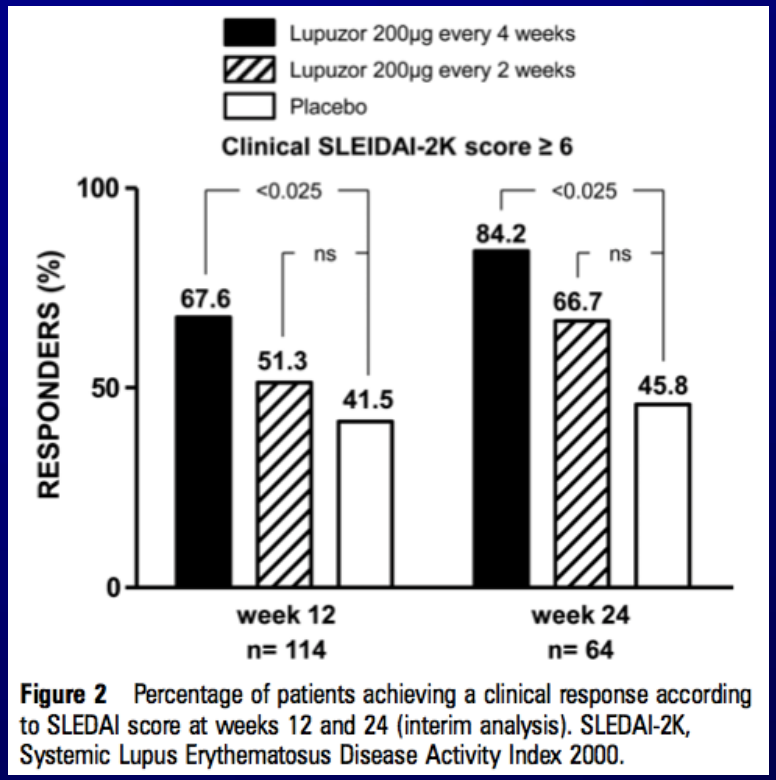
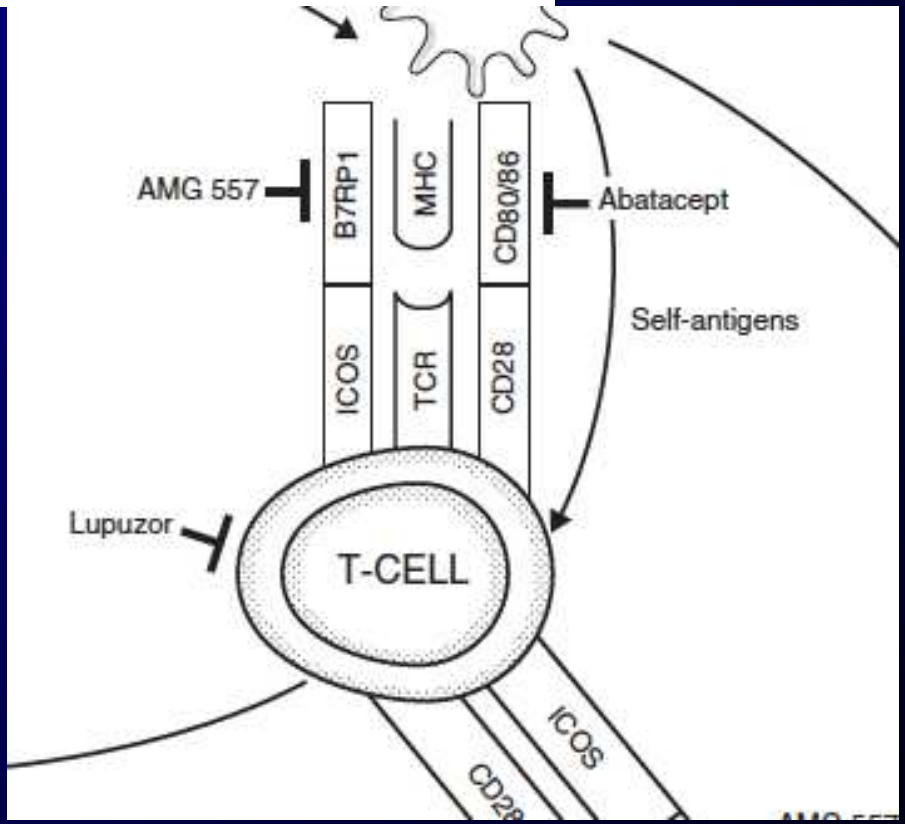
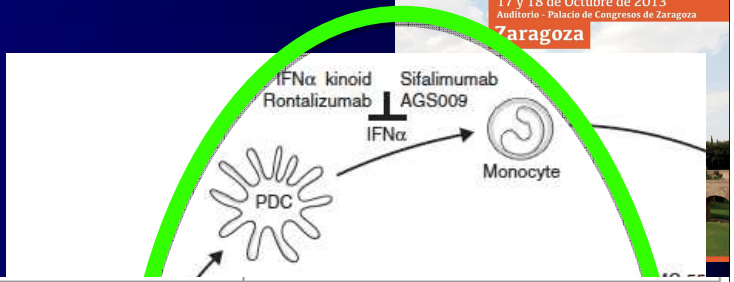


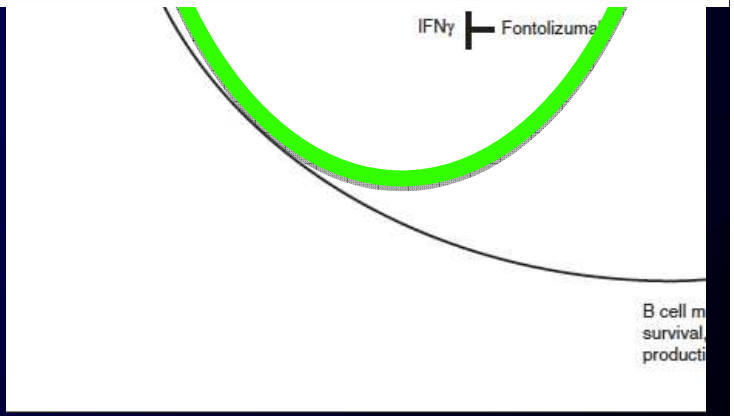
Figure 2 Percentage of patients achieving a clinical response according to SLEDAI score at weeks 12 and 24 (interim analysis). SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.



“Anti-cytokine targeted therapies” en LES



Cytokines	Sifalimumab	IFN-alpha inhibitor	Phase I [104]: SLE Phase II, Phase IIb [105,106]*: SLE	Preliminary efficacy observed
Cytokines	Rontalizumab	IFN-alpha inhibitor	Phase I [107]: SLE Phase II (ROSE) [108]: SLE	N/A No
Cytokines	Tocilizumab	Humanized monoclonal antibody against IL-6 receptor	Phase I [114]: SLE	Preliminary efficacy observed
Cytokines	B-N10	Murine anti-IL-10 monoclonal antibody	Phase I [115]: SLE	Preliminary efficacy observed
Cytokines	Infliximab	Chimeric TNF-alpha inhibitor	Phase I (two trials) [116,117]: SLE Phase II/III (TRIAL) [121]: SLE	Preliminary efficacy observed No (study prematurely terminated)
Cytokines	Etanercept	Soluble TNF-receptor fusion protein	Phase II [122]: SLE	No (study prematurely terminated)



Y aún hay más “targeted therapies” en LES

Anti-Complemento:
•Eculizumab (anti-C5)

FcĐ receptor IIB
Laquinimod
Inhibidores JAK (Janus kinase): Tofacitinib
Inhibidores SyK (Spleen tyrosine kinase): Fosfamatinib

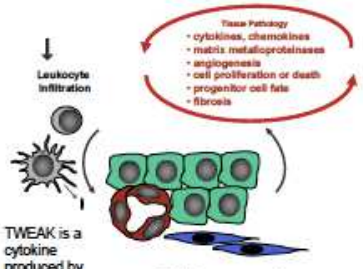
Anti-TWEAK

ATLAS Study: Anti-TWEAK in Lupus Nephritis Study

Study Advisory Committee: Brad Rovin MD (The Ohio State University), David Jayne MD FRCP (Cambridge University, UK), Eduardo Mysler MD (OMI, Argentina), David Wofsy MD (UCSF), Nicolas Wisniacki MD PhD (Biogen Idec)

Rationale for targeting TWEAK in lupus nephritis

Fn14 is highly induced on epithelial and mesenchymal cells in injured and diseased tissue



TWEAK acts on renal cell types: mesangial, podocytes, vascular and tubular cells

Inflammation
- adhesion molecules
- cytokines
- chemokines
- MMPs

Tissue pathology
- mesangial proliferation
- endothelial proliferation
- kidney cell death
- fibrosis

→ Anti-TWEAK not generally immunosuppressive.
- Fn14 not expressed on T or B cells. Anti-TWEAK is not expected to impair systemic adaptive immune responses.
- Potential add on to standard of care without increased risk of infection.

Multiple *in vivo* mouse models have validated targeting of TWEAK/Fn14 for lupus nephritis

ATLAS Study objectives

Primary Objective
- Assess the efficacy of BIIB023 as an add-on treatment to background therapy compared with placebo in combination with background therapy in the treatment of subjects with active biopsy-proven LN.

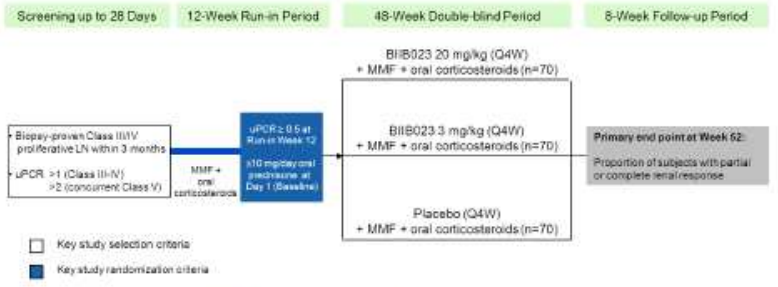
Secondary Objectives
- Assess the safety and tolerability of BIIB023 compared with placebo.

Exploratory Objectives
- Assess the effect of BIIB023 on the histology of repeat renal biopsies.
- Assess the effect of BIIB023 on extra-renal SLE disease activity/manifestations.
- Assess the PK and immunogenicity of BIIB023 in this patient population.

ATLAS Study – Global study

Multicentre – Multinational study
- 27 Countries
- 150 sites

Study Design



Primary endpoint: Achievement of complete or partial response

Complete renal response:
- Urinary protein:creatinine ratio (uPCR) <0.5 with ≥50% reduction of uPCR from Baseline and estimated eGFR within normal range.

Partial renal response:
- ≥50% reduction in uPCR from Baseline with one of the following: a) uPCR of <1.0 if the Day 1 (Baseline) was ≤3.0, or b) uPCR <3.0 if the Day 1 (Baseline) ratio was >3.0; and stabilization of renal function (eGFR ± 25% of Day 1 (Baseline) or serum creatinine within normal range).

Study population

Key Study Inclusion Criteria:
- Diagnosis of SLE: At least 4 ACR criteria must be documented, 1 of which must be a positive antinuclear antibody (ANA), anti-Sm, or anti-dsDNA antibody.
- Diagnosis of ISN/RPS 2003 Class III or IV LN with either active or active/chronic disease, confirmed by biopsy within 3 months prior to screening and active LN at screening. Subjects are permitted to have co-existing Class V. The local histological diagnosis must be confirmed by the central study pathologist.
- Must have proteinuria at Screening defined as:
  - uPCR >1.0 at screening in subjects with biopsy Class III or IV.
  - uPCR >2.0 in subjects with concurrent/co-existing Class V

Randomization criteria (to enter the Double-blind treatment Period)
- Must have uPCR >0.5 g/day at the end of the Run-In period (Run-In Week 12)
- Subjects with a ≥30% increase in serum creatinine from Screening (measured by 2 successive measurements separated by ≥4 weeks) and with creatinine values outside normal range at Run-in Week 12 will be excluded
- Subjects on oral prednisone ≤10 mg/day (or equivalent) at Day 1 of the Double-blind treatment Period

Summary

- BIIB023 potential beneficial effects include reduction of inflammation and unique tissue protective mechanism of action
  - Favorable safety profile makes it well suited for add-on therapy to current agents
- ATLAS study will assess incremental effect of BIIB023 added to standard of care on renal response rate, renal histology and biomarker readouts.

Contact information:
Meredith Schiller
Clinical Trial Manager
Meredith.Schiller@biogenidec.com
Nicolas Wisniacki MD PhD
Medical Director
nicolas.wisniacki@biogenidec.com

ClinicalTrials.gov Identifier: NCT01499355

Study sponsored by: biogen idec

Son seguros? RTX

Efficacy and safety of rituximab therapy for systemic lupus erythematosus: a systematic review and meta-analysis

Lan LAN, Fei HAN, Jiang-hua CHEN[†‡]

(*Department of Kidney Disease Center, the First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou 310003, China*)

[†]E-mail: chenjianghua@zju.edu.cn

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Table 6 Adverse effects in 111 SLE patients

Adverse effect	Number of patients
Severe allergic reaction	11 (9.9%)
Acute infusion reaction	21 (18.9%)
Delayed infusion reaction	2 (1.8%)
Severe sickness	7 (6.2%)
Infection	70 (63.1%)
Urinary tract infection	15 (21.5%)
Respiratory infection	9 (12.3%)
Candidiasis infection	2 (2.9%)
Chickenpox	1 (1.5%)
Bacteremia	3 (4.4%)
Septicemia	1 (1.5%)
Not clear	39 (55.8%)

Son seguros? RTX

Díaz-Lagares *et al. Arthritis Research & Therapy* 2011, **13**:R112
http://arthritis-research.com/content/13/4/R112

arthritis research&therapy

RESEARCH ARTICLE Open Access

Rates of, and risk factors for, severe infections in patients with systemic autoimmune diseases receiving biological agents off-label

Table 2 Rates of all severe infections, according to agent, number of courses, and main autoimmune diseases

	Patients	Person-years	Number of infections	Rate of infections/ 1,000 person-years	95% Confidence interval
TOTAL	344	495	45	90.90	66.31 to 121.64
RITUXIMAB					
- Total	264	328.83	37	112.52	79.20 to 155.10
- First course	211	252.17	30	119.00	88.03 to 169.80
- Second course	38	54.58	2	36.64	4.44 to 132.37
- Third or subsequent courses	15	22.08	5	226.40	73.50 to 528.50

Table 4 Meta-analysis of adverse events in randomized controlled trials of biological agents in patients with systemic autoimmune diseases

	Disease	Patients (n)		Total side effects (n)		Total infections (n)		Severe infections (n)	
		Placebo	*Biologic*	*Placebo*	*Biologic*	*Placebo*	*Biologic*	*Placebo*	*Biologic*
Meijer et al [3]	Sjögren síndrome	10	20	4	16	4	11	NS	NS
Dass et al [4]	Sjögren síndrome	9	8	0	4	0	1	0	1
Merrill et al [5]	SLE	88	169	73	139	15	16	15	16
Stone et al [6]	ANCA-vasculitis	98	99	33	31	NS	NS	7	7
Jones et al [7]	ANCA-vasculitis	11	33	NS	NS	7	19	3	7
RITUXIMAB		216	329	110/205	190/296	26/118	47/230	25/206	31/309
				*HR 1.55 (1.06-2.26)**		*HR 0.97 (0.80-1.17)*		*HR 0.81 (0.45-1.48)*	

Son seguros? BLM

ARTHRITIS & RHEUMATISM
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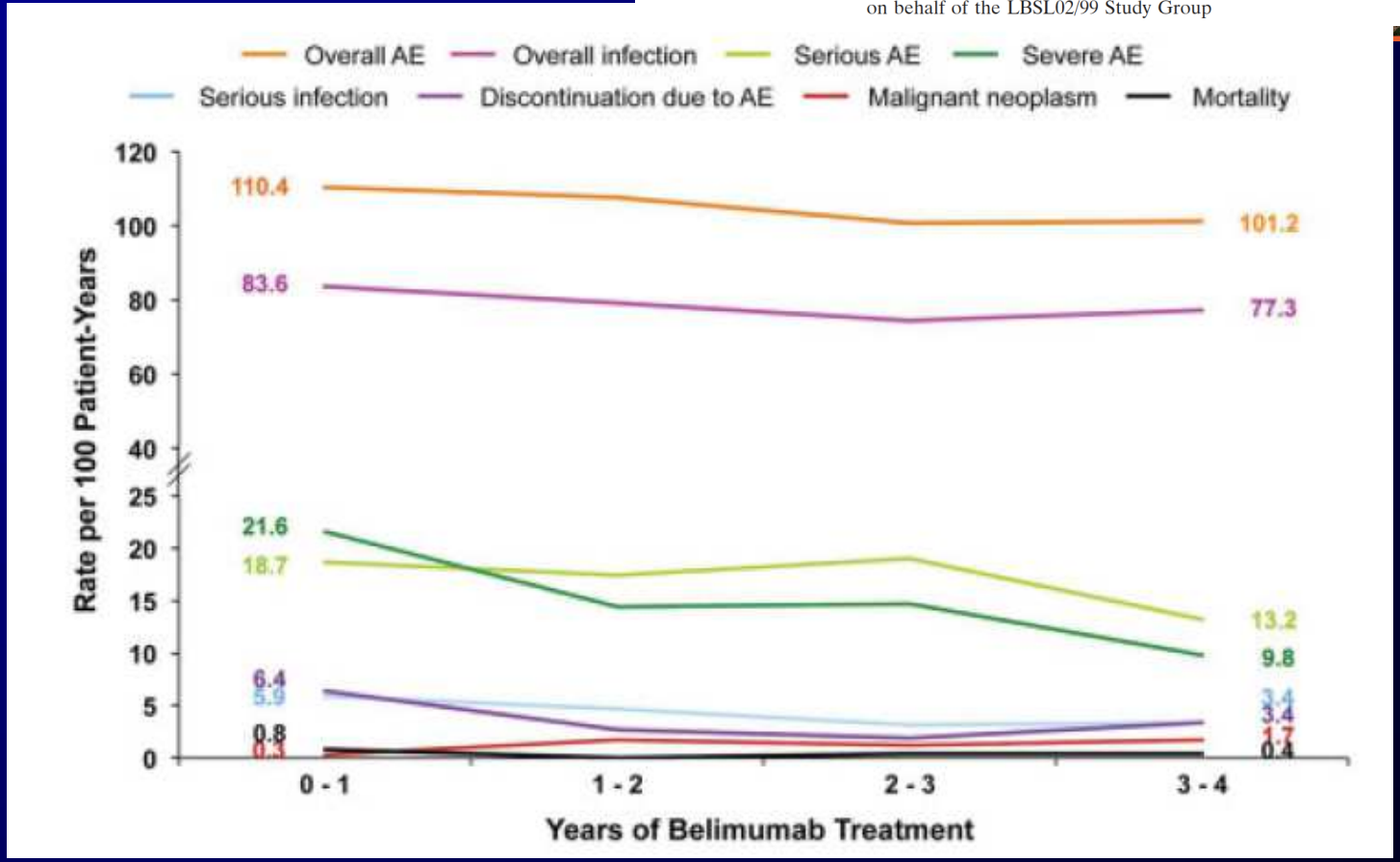
DOI 10.1002/art.34564

Long-Term Safety Profile of Belimumab Plus Standard Therapy in Patients With Systemic Lupus Erythematosus

Joan T. Merrill,[1] Ellen M. Ginzler,[2] Daniel J. Wallace,[3] James D. McKay,[4] Jeffrey R. Lisse,[5] Cynthia Aranow,[6] Frank R. Wellborne,[7] Michael Burnette,[8] John Condemi,[9] Z. John Zhong,[10] Lilia Pineda,[10] Jerry Klein,[10] and William W. Freimuth,[10] on behalf of the LBSL02/99 Study Group



Son seguros? BLM

P168

Sustained Disease Improvement and Safety Profile Over 1745 Patient-Year Experience (7 years) With Belimumab in Patients With Systemic Lupus Erythematosus

Merrill JT[1], Furie RA[2], Wallace DJ[3], Stohl W[4], Chatham WW[5], Weinstein A[6], McKay JD[7], Ginzler EM[8], Freimuth WW[9], MA Petri[10]

AE Incidence (/100 pt-y) With Belimumab	*Interval 1 (0-1y)*	*Interval 2 (1-2y)*	*Interval 3 (2-3y)*	*Interval 4 (3-4y)*	*Interval 5 (4-5y)*	*Interval 6 (5-6y)*	*Interval 7 (6-7y)*
Patients, n (pt-y)	336 (320.1)	339 (299.1)	274 (258.1)	248 (234.2)	223 (215.8)	208 (197.6)	190 (167.0)
Overall AEs	326 (101.8)	322 (107.7)	260 (100.8)	237 (101.2)	211 (97.8)	191 (96.7)	172 (103.0)
Serious AEs	55 (17.2)	52 (17.4)	49 (19.0)	31 (13.2)	41 (19.0)	32 (16.2)	30 (18.0)
Overall infections	254 (79.4)	237 (79.2)	192 (74.4)	181 (77.3)	145 (67.2)	126 (63.8)	128 (76.6)
Serious infections	17 (5.3)	14 (4.7)	8 (3.1)	8 (3.4)	6 (2.8)	8 (4.0)	5 (3.0)
Malignancies[a]	0	3 (1.0)	2 (0.8)	1 (0.4)	3 (1.4)	2 (1.0)	1 (0.6)
Mortality	3 (0.8)	0	1 (0.4)	1 (0.4)	0	0	2 (1.2)

aExcluding nonmelanoma skin cancer; including unspecified lung malignancy.

CAUSES OF DEATH:

- aspiration pneumonia with subsequent sepsis and respiratory failure
- infection
- cardiovascular disease
- suicide
- osteomyelitis with subsequent respiratory failure
- B-cell lymphoma

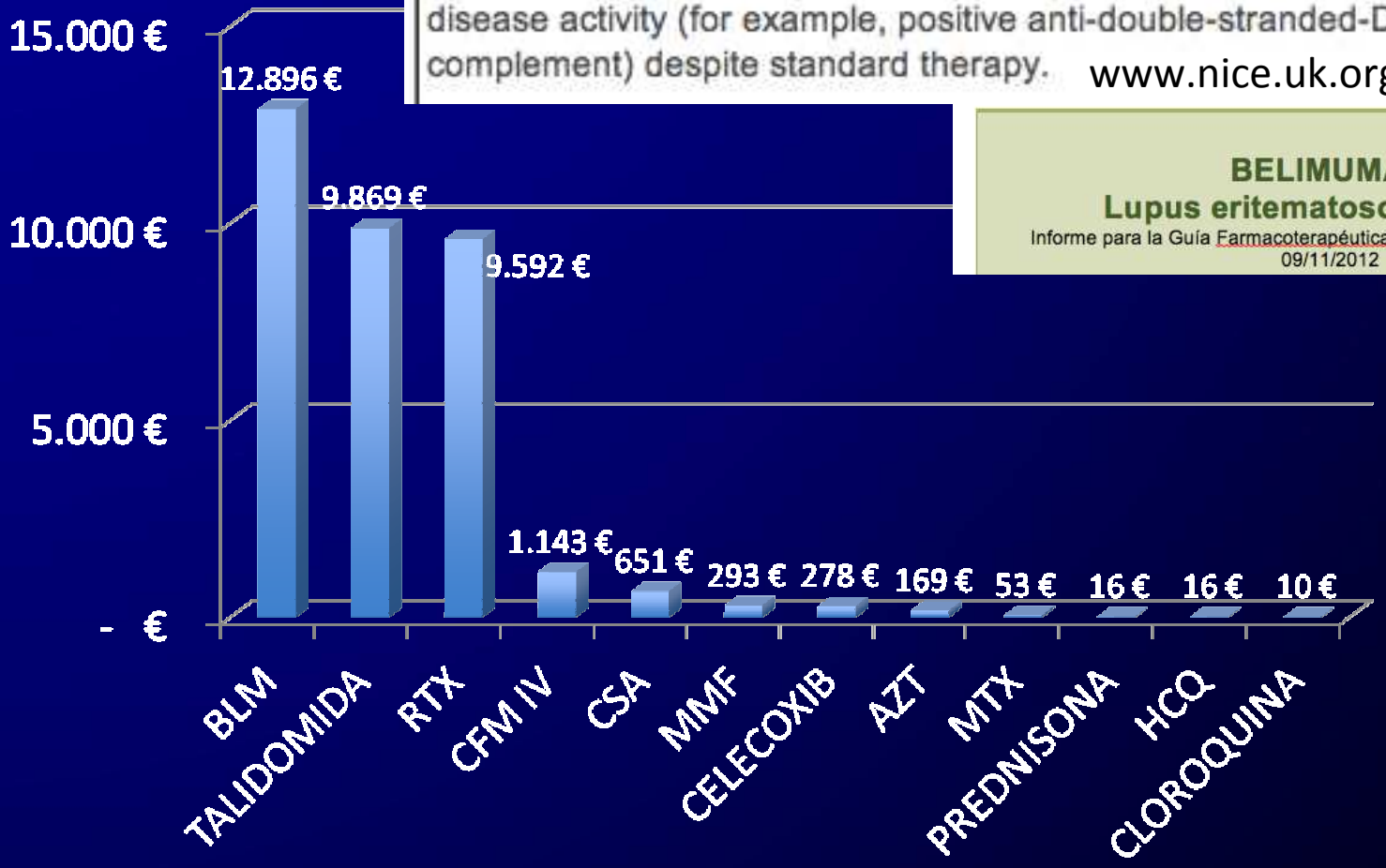
Son caros?

Summary of Appraisal Committee's key conclusions

TAXXX	Appraisal title: Belimumab for the treatment of active autoantibody-positive systemic lupus erythematosus
Key conclusion	
Belimumab is not recommended as add-on therapy in adult patients with active, autoantibody-positive systemic lupus erythematosus with a high degree of disease activity (for example, positive anti-double-stranded-DNA and low complement) despite standard therapy.	

www.nice.uk.org

Coste anual tto



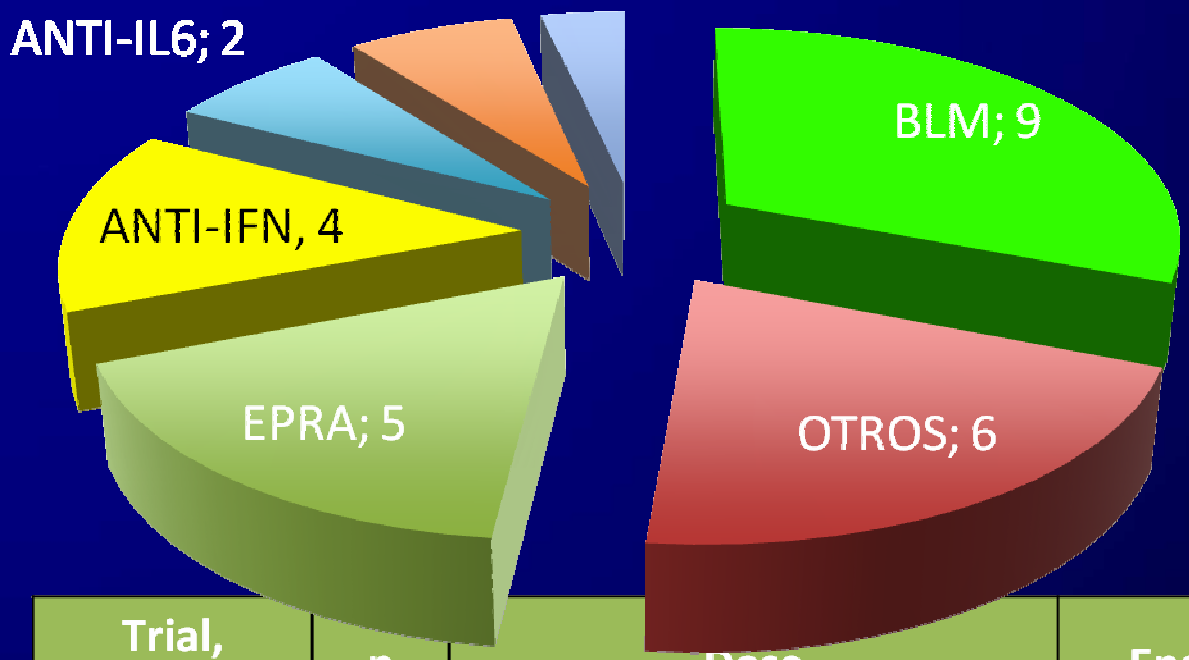
BELIMUMAB
Lupus eritematoso sistémico
Informe para la Guía Farmacoterapéutica de Hospitales de Andalucía
09/11/2012

Futuro: BIOLÓGICO IDEAL ="IDEAL4LESMAB"

Adm vo, sc
Dosis única, repetible
Alta eficacia en:
•Clínica en todos índices (SLEDAI, BILAG, PGA, SRI…)
•Prevención de brotes (TTF)
•biológica (nDNA, C3, C4, RFAs…)
•reducción dosis corticoides (inmn-)
Eficacia sostenida
Bien tolerado, seguro, sin infecciones
Sin precisar monitorización (Igs, CD20…)
Bajo coste
Uso aprobado x FDA, EMEA, AEMS, comités de hospitales → no precisar papeleo
Producción española, diseño aragonés

Futuro próximo

www.clinicaltrials.gov 1-10-13



Trial, PHASE	n	Dose	Endpoint	Ends
BLISS-SC, III	816	544 SOC + BLM 200 mg SC/w 272 SOC + placebo	SRI at 52w	Oct'14-Jun'15

ASÍ PUES…

- Biológicos en LES = “targeted therapies”
- EFICACES EN DETERMINADOS ESCENARIOS
- VIGILAR APARICIÓN INFECCIONES
- SEGUROS A LARGO PLAZO
- ATENCIÓN A PRÓXIMOS ENSAYOS (BLM, RTX, EPRA)

TAKE-HOME MESSAGES

- Hay que poner biológicos a todos los pacientes con LES, van mejor
- Nunca hay que utilizar biológicos, no son coste-efectivos

TAKE-HOME MESSAGES

- Hay que poner biológicos a todos los pa
  van mejor
- Nunca hay que utilizar biológicos, no son coste-efectivos
- Podemos usar biológicos en pacientes LES en que la evidencia sea favorable a dichos tratamientos, con bajo riesgo.
- Algunos biológicos pueden ser útiles en LES refractarios, según varios registros internacionales y experiencia de múltiples centros.

UEAS

Dr. José Velilla Marco
Dr. Luis Sáez Comet
ATS Lola Pamplona Neri

Unidad de Enfermedades Autoinmunes Sistémicas
Servicio de Medicina Interna
Hospital Universitario Miguel Servet de Zaragoza
Edificio de Consultas Externas
C/Padre Arrupe, s/n
50009 Zaragoza
Tel 976765500 ext 2799
e-mail: ueas.servet@salud.aragon.es

Table 3. Primary ARDs among 34 patients who developed PML during immunosuppressive therapy for ARD*

Primary ARD	Total no. of patients	No. taking biologic agents	No. taking synthetic agents only
SLE	17	5	12
RA	10	7	3
DM	3	1	2
CV	2	2	0
GPA	2	0	2
Total	34	15	19

* The primary autoimmune rheumatic disease (ARD) was the disease for which immunosuppressive agents were primarily prescribed. Eight patients had a secondary rheumatic disease: Sjögren's syndrome in 6, rheumatoid arthritis (RA) in 1, and dermatomyositis (DM) in 1. PML = progressive multifocal leukoencephalopathy; SLE = systemic lupus erythematosus; CV = cryoglobulinemic vasculitis; GPA = granulomatosis with polyangiitis (Wegener's).

ARTHRITIS & RHEUMATISM
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DOI 10.1002/art.34468

Progressive Multifocal Leukoencephalopathy Associated With Immunosuppressive Therapy in Rheumatic Diseases

Evolving Role of Biologic Therapies

Eamonn S. Molloy[1] and Leonard H. Calabrese[2]