APPROCCI INTERDISCIPLINARI IN REUMATOLOGIA

4ª edizione

INFETTIVOLOGIA E MALATTIE REUMATICHE

Torino 7-8 ottobre 2016

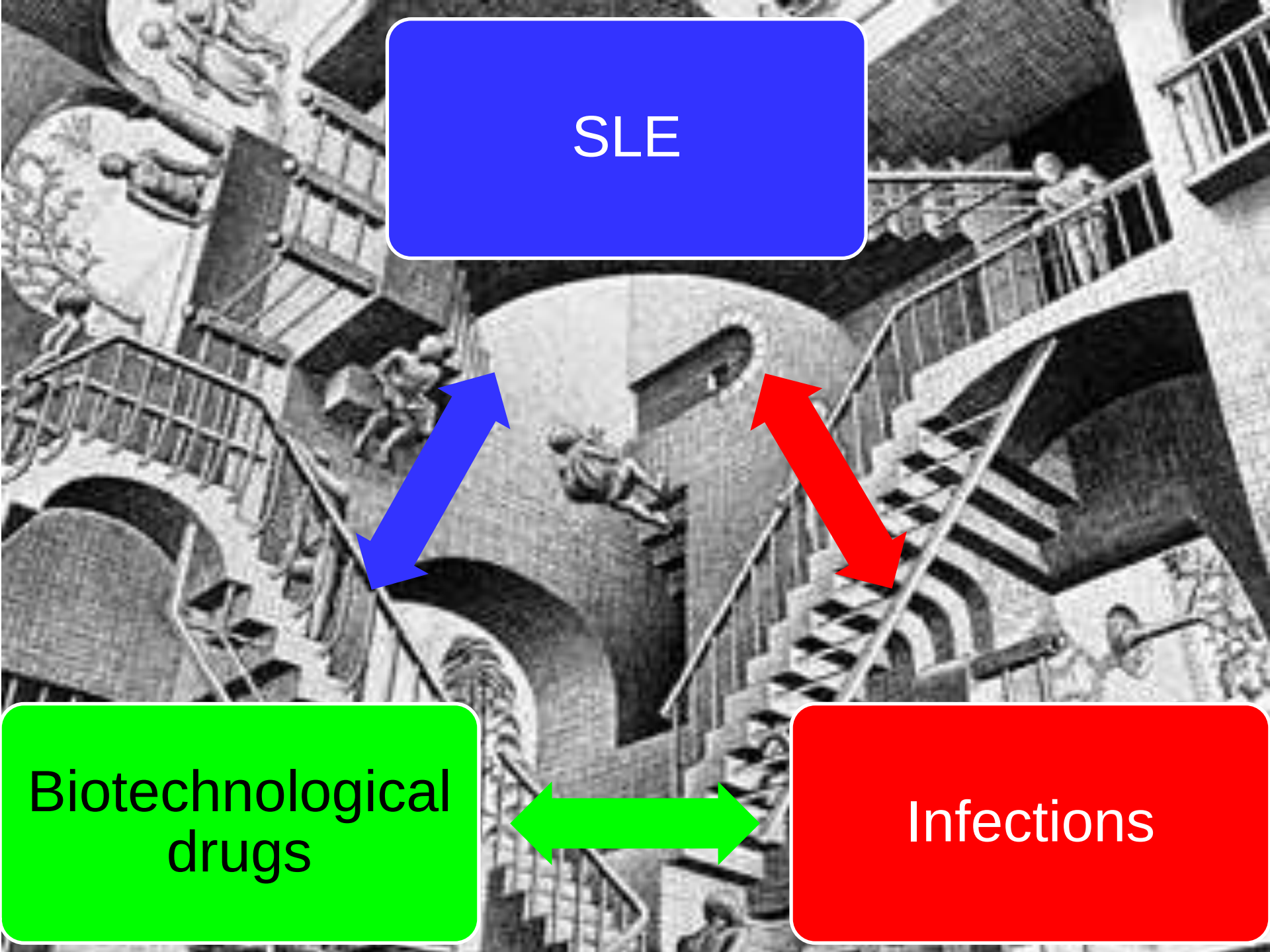
Alma Ticinensis Universitas

Ospitale di S. Matteo

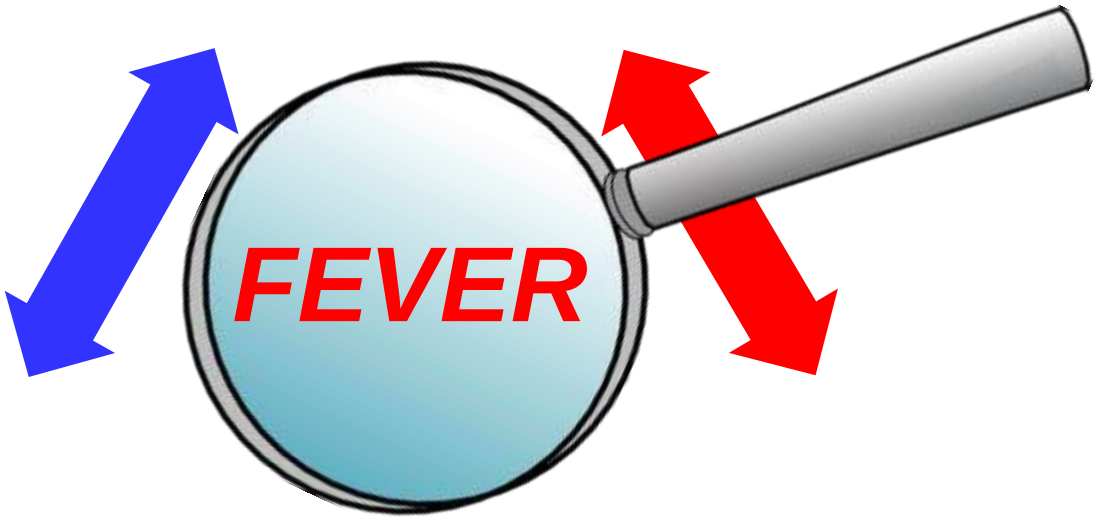
Farmaci biologici nel LES

Dr Lorenzo Cavagna

Divisione di Reumatologia, Università e Fondazione IRCCS Policlinico S. Matteo, Pavia


SLE
Biotechnological drugs
Infections

SLE



Biotechnological drugs

Infections

American College of Rheumatology The 1982 revised criteria for classification of systemic lupus erythematosus

Derivation and validation of SLICC classification criteria for systemic lupus erythematosus

FEVER IS NOT AMONG SLE CLASSIFICATION CRITERIA

Tan EM, et al. Arthritis Rheum 1982
Hochberg MC et al Arthritis Rheum 1997

Petri M, et al. Arthritis Rheum 2012

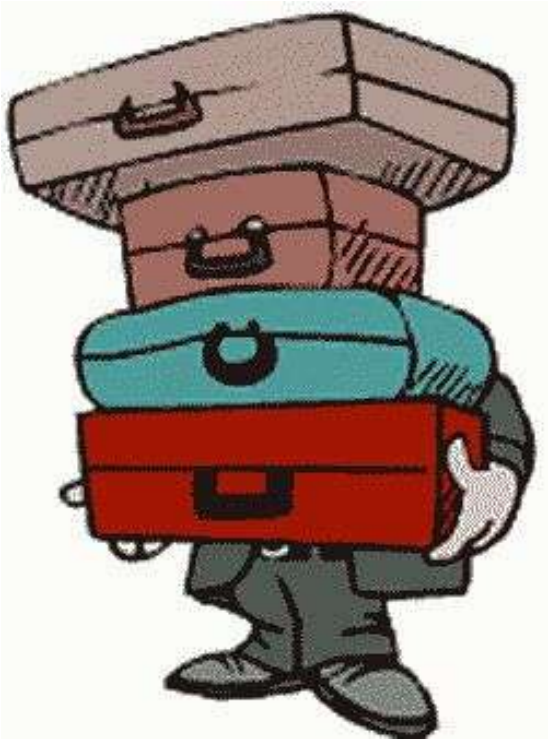
SLE Disase Activity Index (SLEDAI) SELENA modification

Descriptor	Weighted score	Descriptor	Weighted score
Seizure	8	New malar rash	2
Psychosis	8	Alopecia	2
Organic brain syndr	8	Mucous membrane	2
Visual	8	Pleurisy	2
Cranial nerve	8	Pericarditis	2
Lupus headache	8	Low complement	2
Cerebrovascular ac	8	anti ds DNA	2
Vasculitis	8	Fever	1
Arthritis	4	Thrombocytopenia	1
Myositis	4	Leukopenia	1
Casts	4		
Hematuria	4		
Proteinuria	4		
Pyuria	4		

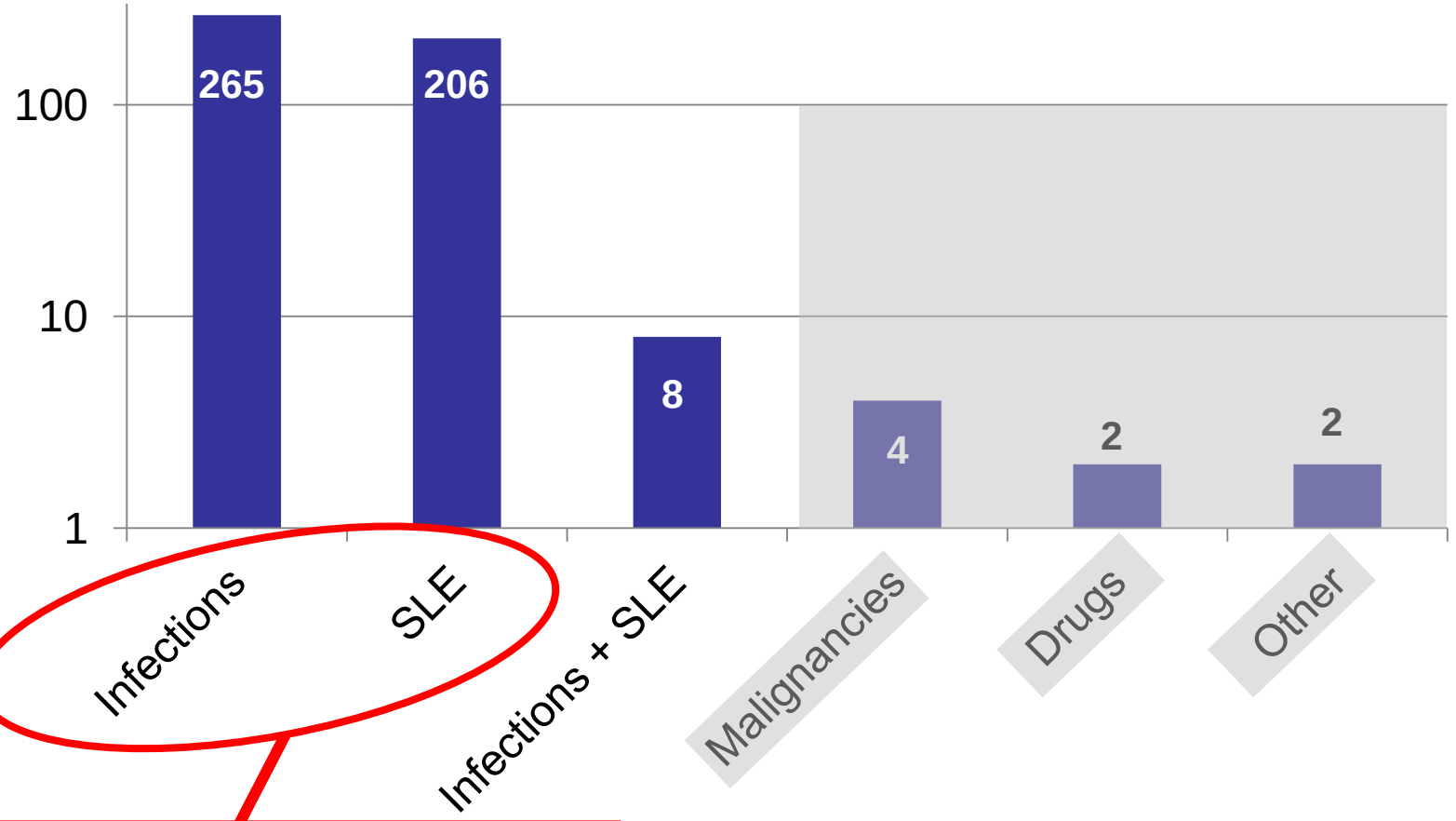
FEVER HAS A LOW WEIGHT IN THE VARIOUS SLE ACTIVITY INDEXES UP TO NOW AVAILABLE

Gladman DD, et al. J Rheumatol 2002;29:288-91

The right weight of things



The causes and clinical significance of fever in systemic lupus erythematosus: a retrospective study of 487 hospitalised patients



more than 95% of causes of fever in hospitalised SLE patients

Adapted from: Zhou WJ, Yang CD. *Lupus 2009;18:807–12.*

SLE fever is observed in particular in patients with serositis, lymphadenopathies, and thrombosis. Conversely discoid lesions are negatively associated with SLE fever

Gomez J, et al. Medicine 2006;85:157–68

SLE fever is common in subacute cutaneous lupus (35% of patients)

Drosos AA, et al. Ann Med Interne 1990;141:421-4.

SLE fever is more common in children than in adult patients with SLE

Livingston B, et al. Lupus 2011;20:1345–55

SLE fever is more common in male than in female SLE (both at the onset and during the follow-up)

Garcia MA, et al. Lupus 2005;14:938–46.

URINARY TRACT IS FREQUENTLY INVOLVED

*Adapted from: Cervera M, et al. Lupus 2009;*18:869–74

SEPSIS ARE NOT SO FREQUENT

*Adapted from: Cervera M, et al. Lupus 2009;*18:869–74

A HIGH PREVALENCE OF SEPSIS RELATED MORTALITY IS DESCRIBED

*Adapted from: Cervera M, et al. Lupus 2009;*18:869–74

In case of infection, mortality rates are higher in adult and late onset with respect to childhood onset SLE

Mok CC et al. Medicine 2005

Epidemiology and clinical outcomes of bloodstream infections among lupus patients

HIGH RATES OF EARLY MORTALITY

"Thirty-eight SLE patients had 48 episodes of significant bacteriaemia, with **a 30-day mortality rate of 6.25%**"

LEADING PATHOGENS ISOLATED

"**Escherichia coli and Staphylococcus aureus** were the leading Gram-negative and Gram-positive pathogens, respectively"

IN CASE OF PREVIOUS BLOODSTREAM INFECTIONS THERE IS A HIGH RISK OF RECURRENCE AND PATIENTS DEATH.

After a median follow-up of 25 months, eight of these 38 patients (**21.1%**) had a **further episode of bacteremia** and 13 of them (**34.21%**) **died**

Marcos M, et al. Lupus 2011;20:965–71.

Viral infections

- ✓ Herpes-Varicella Zoster
  - Disseminated herpes zoster infection occur in as many as 11% of cases
- ✓ HSV,
- ✓ EBV, CMV
- ✓ Polyomaviruses (JCV, BKV)
- ✓ Human Papilloma Virus
- ✓ Parvovirus B19

Fungal infections

- ✓ *Candida* sp.
  - Oral thrush or esophageal moniliasis
  - Visceral candidiasis
- ✓ *Criptococcus neoformans*
- ✓ *Aspergillus* sp.
  - Pneumonia
  - Meningitis, septicemia
- ✓ *Pneumocystis jirovecii*

Parasitic and protozoan infestations

- ✓ Strongyloides stercoralis
- ✓ Toxoplasma
- ✓ Leishmania

Wilcox MH et al. Ann Rheum Dis 1990

Wallis PJ et al. Ann Rheum Dis 1983

Kang I et al Curr Opin Rheumatol 2003

Livneh A et al. Arthritis Reum 1988

Fever assessment in established SLE

Clinical presentation

- Childood onset SLE

Livingston B, et al. Lupus 2011

- *Subacute cutaneous lupus*

Drosos AA, et al. Ann Med Interne 1990

- *Male SLE*

Garcia MA, et al. Lupus 2005

- *Serositis, kidney, cytopenia, lymphadenopathies, thrombosis, anti-Ro*

Gomez J, et al. Medicine 2006

- Chronic steroid therapy

Rovin BH et al. Kidney Int 2005

- Shacking chills fever

Stahl NI et al. Am J Med 1979

- Adult/late SLE onset

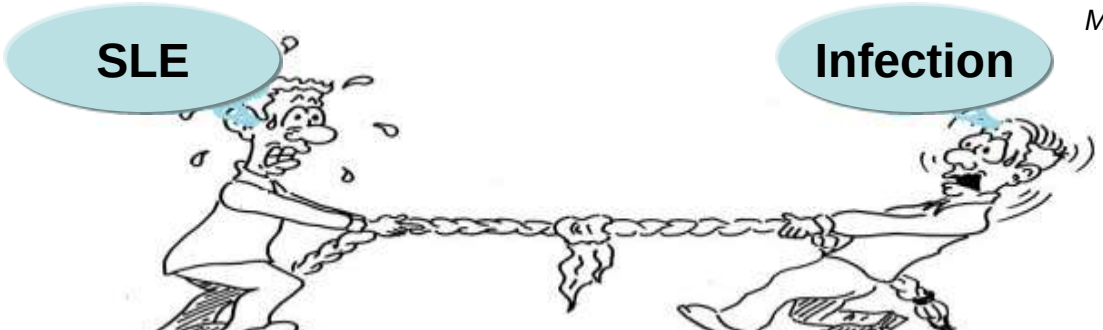
Stahl NI et al. Am J Med 1979

- *Previous/actual healthcare contacts*

Marcos M, et al. Lupus 2011

- *Previous* episodes of bacteremia

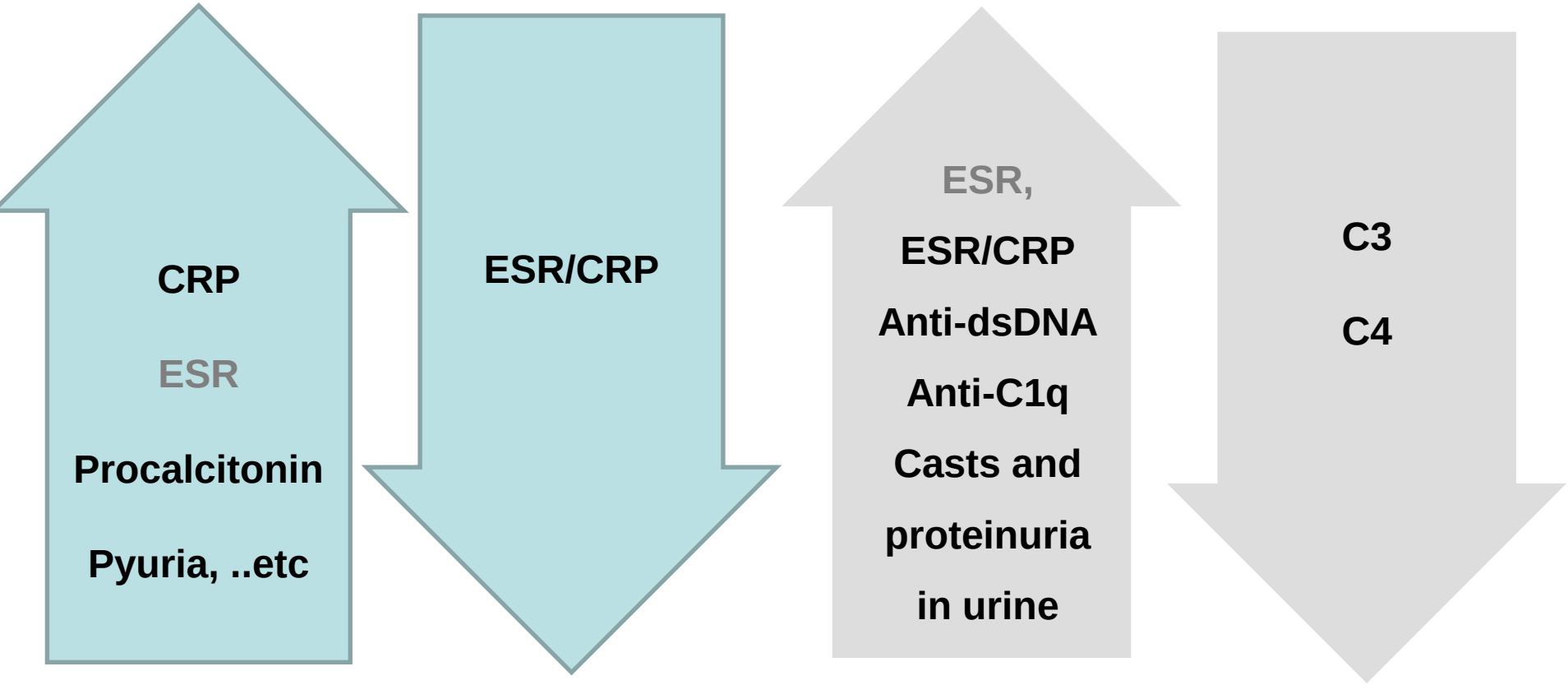
Marcos M, et al. Lupus 2011



Differential diagnosis

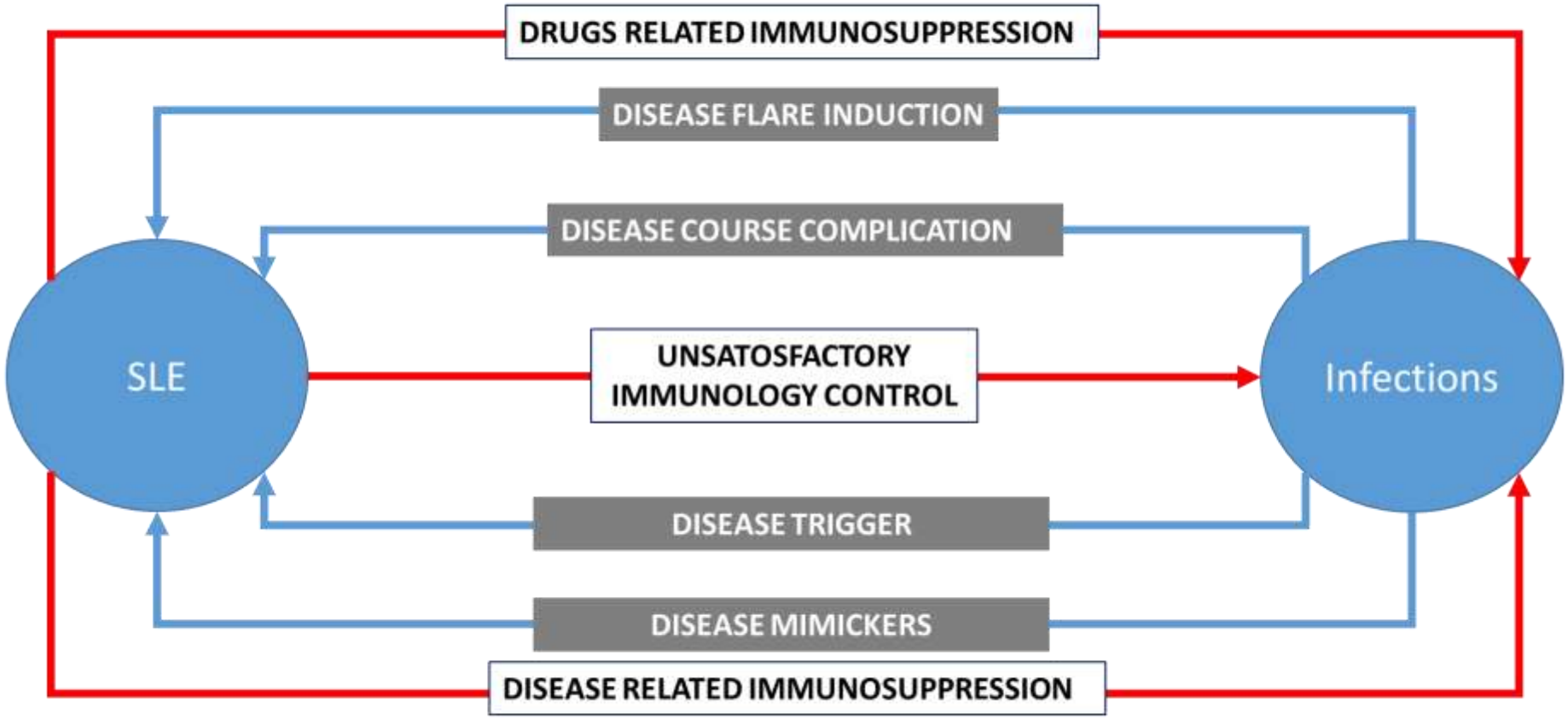
- **Microbiologic and radiological procedures**
- **Laboratory analysis**
  - Acute phase reactants (ESR, CRP, ESR/CRP, WBC)
  - Procalcitonin
  - Anti ds-DNA, anti-C1q, proteinuria, casts at urinalysis
  - other

Conventional markers in SLE patients



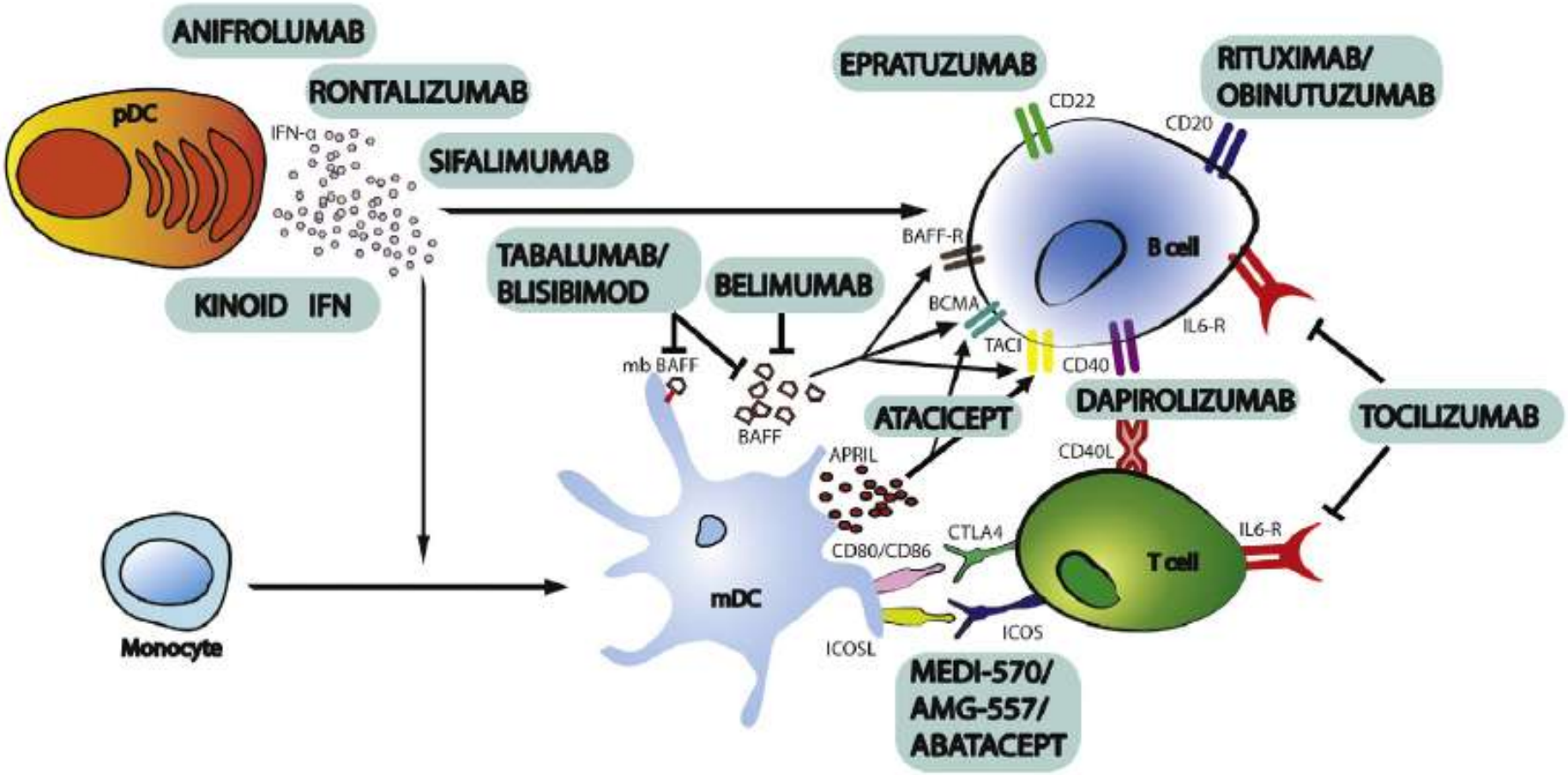
Adapted from: Sciascia S, et al. Autoimmun Rev 2012;12:157-63.

SLE and virus infections: how many cutting hedges have the sword?



Doaty S, et al. **Infection and Lupus: Which Causes Which? Curr Rheumatol Rep** 2016 Mar;18:13. doi: 10.1007/s11926-016-0561-4.

Biotechnological drugs in SLE



Lazaro E, et al. Joint Bone Spine 2016 Sep 20. pii: S1297-319X(16)30123-3

Biotechnological drugs in SLE

Belimumab

Human monoclonal IgGλ antibody against B-lymphocyte stimulator (BLyS) blocking soluble BLyS.

Indicazioni in Italia: come terapia aggiuntiva nei pazienti adulti con lupus eritematoso sistemico (LES) attivo, autoanticorpi-positivo, con un alto grado di attività della malattia (ad esempio anti-dsDNA positivi e basso complemento) nonostante la terapia standard

Rituximab

Anti-CD20 human-murine monoclonal chimeric antibody causing selective short-term depletion of matured B cells through 1) induction of apoptosis, 2) complement-dependent cytotoxicity,3) antibodydependent cytotoxicity

Fallimento EXPLORER (LES extrarenale da moderato a severo) e LUNAR (NL classe III o IV). ANALISI POST-HOC EXPLORER: riduzione flare gravi di malattia + studi non controllati a favore del farmaco. Linee guida ACR trattamento NL (no prima linea)

Belimumab

Infezioni

I medici devono esercitare cautela quando prendono in considerazione l’uso di Benlysta nei pazienti con infezioni severe o croniche o con anamnesi positiva per infezioni ricorrenti. I pazienti che sviluppano un' infezione mentre sono in trattamento con Benlysta devono essere attentamente monitorati e si deve considerare l'interruzione della terapia con medicinali immunosoppressori, incluso belimumab, fino alla risoluzione dell'infezione.

Non è noto il rischio relativo all’uso di Benlysta nei pazienti con tubercolosi attiva o latente.

Benlysta non è stato studiato nei seguenti gruppi di pazienti, nei quali non è raccomandato:

- **HIV, anamnesi positiva, o malattia in corso, per epatite B o C**

http://www.ema.europa.eu/docs/it_IT/document_library/EPAR_-_Product_Information/human/002015/WC500110150.pdf

Safety profile of belimumab: pooled data from placebo-controlled phase 2 and 3 studies in patients with systemic lupus erythematosus.

	Standard therapy +			
	Placebo ($n=675$), %	Belimumab 1 mg/kg ($n=673$), %	Belimumab 4 mg/kg[a] ($n=111$), %	Belimumab 10 mg/kg ($n=674$), %
Infections				
≥1 infection	67.4	71.9	79.3	70.8
≥1 serious infection[b]	5.5	7.1	6.3	5.3
≥1 severe infection[c]	3.4	3.9	5.4	2.7
Infection resulting in discontinuation	1.2	0.7	0.9	0.6
Infection resulting in death	0.1	0.1	0	0.4
Infections of special interest				
Cellulitis	6.7	8.9	8.1	6.4
Sepsis	0.4	0.6	0.9	0.7
Fungal	3.4	3.1	3.6	2.5
Herpes virus	8.0	8.3	4.5	6.8
All respiratory	49.5	52.0	59.5	53.0
Upper respiratory	44.4	45.0	55.0	45.8
Lower respiratory	8.9	11.9	11.7	12.3
Pneumonia	2.7	3.3	1.8	2.4
Opportunistic	0	0	0	0.3[e]

These data support the conclusion that belimumab in combination with standard SLE therapy was generally well tolerated in a predominantly autoantibody positive population with active SLE.

Wallace DJ, et al. Lupus 2013;22:144-54

Long-term organ damage accrual and safety in patients with SLE treated with belimumab plus standard of care

"Patients with SLE treated with long-term belimumab plus SoC had a low incidence of organ damage accrual and no unexpected AEs. High-risk patients with pre-existing organ damage also had low accrual, suggesting a favorable effect on future damage development."

Bruce IN, et al. Lupus 2016;25:699-709.

Rituximab

Infezioni

MabThera non deve essere somministrato ai pazienti con infezione attiva grave (ad es. **tubercolosi**, sepsi e infezioni opportunistiche). I medici devono essere cauti quando prendono in considerazione l'uso di MabThera in pazienti con **storia di infezioni ricorrenti o croniche** o con condizioni di base che possono ulteriormente **predisporre i pazienti a infezioni gravi**.

Casi di **riattivazione di epatite B** sono stati riportati in soggetti che hanno ricevuto MabThera incluse segnalazioni di epatite fulminante ad esito fatale. La maggior parte di questi soggetti riceveva anche chemioterapia citotossica…….Lo screening del virus dell'epatite B (HBV) deve essere effettuato in tutti i pazienti prima dell'inizio del trattamento con MabThera e dovrebbe **almeno includere il dosaggio dell'HBsAg e dell'HBcAb**……..I pazienti con **sierologia positiva per epatite B** (sia HBsAg che HBcAb) devono essere **valutati da un clinico epatologo** prima dell'inizio del trattamento e devono essere monitorati e seguiti secondo gli standard clinici locali per prevenire la riattivazione dell'epatite B.

http://www.ema.europa.eu/docs/it_IT/document_library/EPAR_-_Product_Information/human/000165/WC500025821.pdf

The effects of rituximab therapy on released interferon-γ levels in the QuantiFERON assay among RA patients with different status of Mycobacterium tuberculosis infection

"No occurrence of active TB or QFT-GIT conversion was observed in patients receiving 1 year of rituximab therapy. No significant effect of rituximab therapy on IFN-γ release levels was observed in patients with LTBI and with anti-TNF-α-associated TB. Rituximab may be an alternative therapeutic agent for these patients."

Chen YM,et al. Rheumatology (Oxford) 2013;52:697-704

Polyomavirus JC infection

Study (Year)	Country or Region	Duration of SLE (yr.)	Gender	Age	Drug exposures at PML diagnosis	Duration of drug use	Other Drug exposures prior to PML diagnosis	PML diagnosis	Outcome of PML
Ahmed et al.[26] (1999)	US	17	F	35	CYC	9 mo	MTX, AZA, CST[a]	MRI, brain biopsy	Died
Akahoshi et al.[27] (1997)	Japan	4	F	35	CST[a], CYC	17 mo	CST[a]	MRI, postmortem brain biopsy	Died
Beppu et al.[28] (2012)	Japan	5 mo	M	67	CST[a]	5 mo	NR	MRI, brain biopsy, CSF(+)	Died
Brandao et al.[29] (2012)	Portugal	6	F	26	None	n/a	RTX, CST[c], HCQ, CYC, AZA, MTX, Immunoglobulins, THD	MRI, CSF (+)	Survived
		5	F	57	CST[b], HCQ, anticoagulant	NR	NR	MRI, brain biopsy	Survived
Calabrese et al.[30] (2007)	US	27	F	42	HCQ	27 yr	CST[a]	MRI, CSF	Died (3 mos)
Damasio et al.[24] (2011) *Abstract*	Portugal	6	F	56	NR	n/a	NR	MRI, brain biopsy	NR
		7	F	28	RTX	NR	NR	MRI, CSF(+)	NR
Fredericks et al.[25] (2014)	US	16	F	40	Belimumab, MMF, CST[b]	0 mo ~1 yr NR	HCQ	MRI, CSF(+)	Died
Goncalves et al.[31] (2011)	Canada	>25	F	52	HCQ, MMF	NR	NR	MRI, CSF (+)	Died
Govindappa et al.[32] (2007)	US	NR	F	49	CST[b], HCQ MMF	1 yr 1 mo	AZA	MRI, brain biopsy	Died
Graff-Radford et al.[33] (2012)	US	6	F	23	ETN, CST[d]	4 yr	HCQ	MRI, CSF(+)	Died
Harris[34] (2008) *Letter*	UK	23	F	45	none	n/a	CST[c], AZA, CYC, RTX	MRI, CSF(+)	Died
Itoh et al.[35] (2006)	Japan	12	F	31	CST[b], AZA	NR	NR	MRI, CSF(+)	Survived
		8	F	40	CST[b]	NR	NR	MRI, CSF(+)	Died
Kinoshita et al.[36] (1998)	Japan	6	F	21	CST[a]	6 yr	NR	Postmortem brain biopsy	Died
Krupp et al.[37] (1985)	US	NR	F	28	CST[c]	NR	NR	brain biopsy	Died
Lefevre et al.[38] (2009)	France	18	F	53	MMF, HCQ, CST[b]	NR	NR	MRI, CSF(+), brain biopsy	Survived
Medin et al.[39] (2012) *Abstract*	US	4 mo	F	55	CST[c], HCQ	4 mo	none	MRI, CSF(+), brain biopsy	NR
Newton et al.[40] (1986)	UK	21	F	57	None	n/a	Synacthen, CST[d]	Postmortem brain biopsy	Died
		13	F	54	CST[a]	NR	CQP, CST[d]	Postmortem brain biopsy	Died
Nived et al.[41] (2008)	Sweden	7	M	27	CYC, CST[b]	n/a	AZA	Postmortem brain biopsy	Died
		7	M	51	AZA, CYC, CST[b]	n/a	NR	MRI, brain biopsy, CSF(+)	Survived with disability
		1	F	57	CYC	n/a	AZA, MMF, MTX, CST[b]	MRI, CSF(+)	Died
Pavlovic et al.[42] (2012)	Serbia	10	F	39	MMF, CST[b]	NR , 2.5 yr	CST[d]	MRI,	Survived
Reilmann et al.[43] (2005)	Germany	20	F	40	CST[b]	NR	CYC, AZA, MMF	MRI, CSF(+), brain biopsy	Survived
Roberts et al.[44] (2007)	US	NR	F	47	CST[c], CYC	NR	none	MRI, brain biopsy	Died

(continued)

RTX

RTX

BLM

RTX

Progressive multifocal leukoencephalopathy in patients with systemic lupus erythematosus: a systematic literature review

Henegar CE, et al. Lupus 2016:25:617–626.

Epstein Barr virus (EBV)

- High prevalence of EBV infection in both healthy subjects and SLE patients: 95% vs 99.5%

James JA, Arthritis Rheum 2001

- Higher prevalence in young SLE patients with respect to control group: 99.6% vs 70%

James JA, J Clin Invest 1997 and McClain MT, Arthritis Rheum 2006

- High prevalence of detectable EBV DNAemia in SLE patients

Mohamed AE, Int J Rheum Dis 2015 and Lu JJ, Lupus 2007

- EBV related complication in SLE patients

Abenavoli L, Int J Immunopathol Pharmacol 2011 and Tsang HH, Lupus 2010

- EBV as a SLE mimicker

Yamashita H, Lupus. 2014

Viruses as potential pathogenic agents in systemic lupus erythematosus

A number of exogenous viruses have been linked to the pathogenesis of SLE, of which EpsteinBarr virus (EBV) has the most evidence of an aetiological candidate.

Nelson P, et al. Lupus 2014;23:596-605

EBV might be able to induce SLE by molecular mimicry because of cross-reaction of EBNA-1 with self-antigens

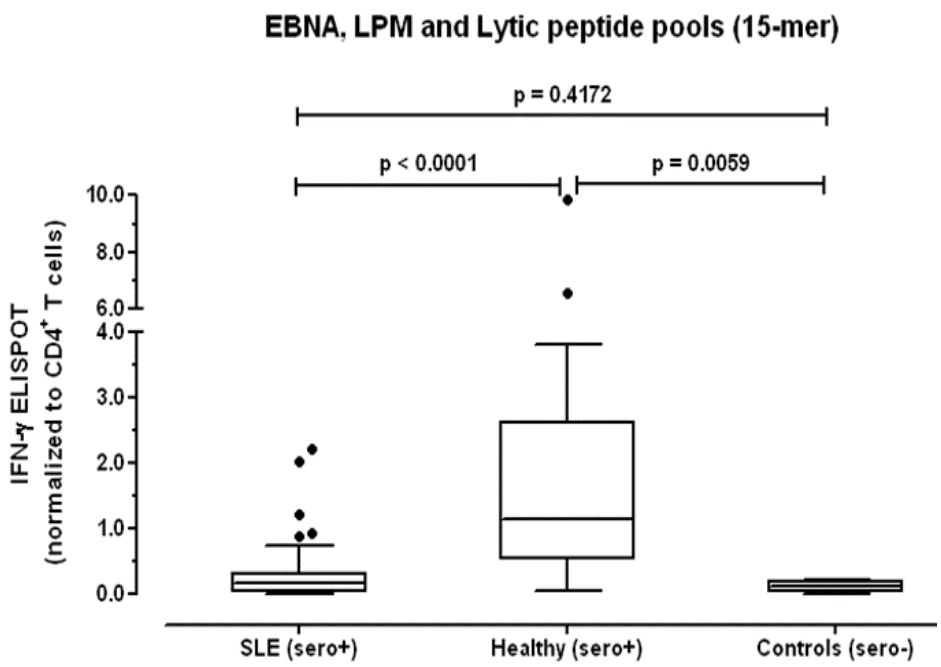
Yadav P, Immun Inflamm Dis 2016 and Poole BD, Autoimmunity 2006 and Harley JB, Bull NYU Hosp Jt Dis 2006

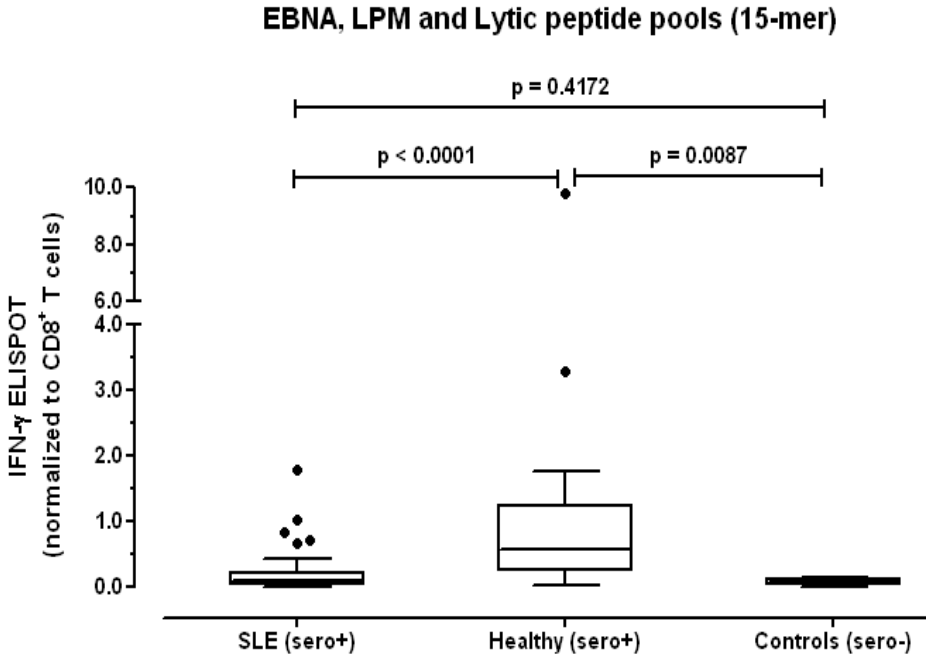
Evaluation of EBV and HCMV-specific T cellular response in SLE patients by using a normalized enzyme- linked immunospot (ELISPOT) assay

	SLE patients (70)	Healthy subjects (50)	p value
Gender (female/male)	64/6	35/15	
Age (years, median [range])	46 [21-75]	44 [19-77]	
EBV-seropositive	68	46	0,233
EBV DNA positive	30	4	<0.001*
EBV DNAemia (copies/mL, median [IQR])	233 [100-656.3]	125 [62.5-225]	0.189

Manuscript in draft

Evaluation of EBV and HCMV-specific T cellular response in SLE patients by using a normalized enzyme- linked immunospot (ELISPOT) assay

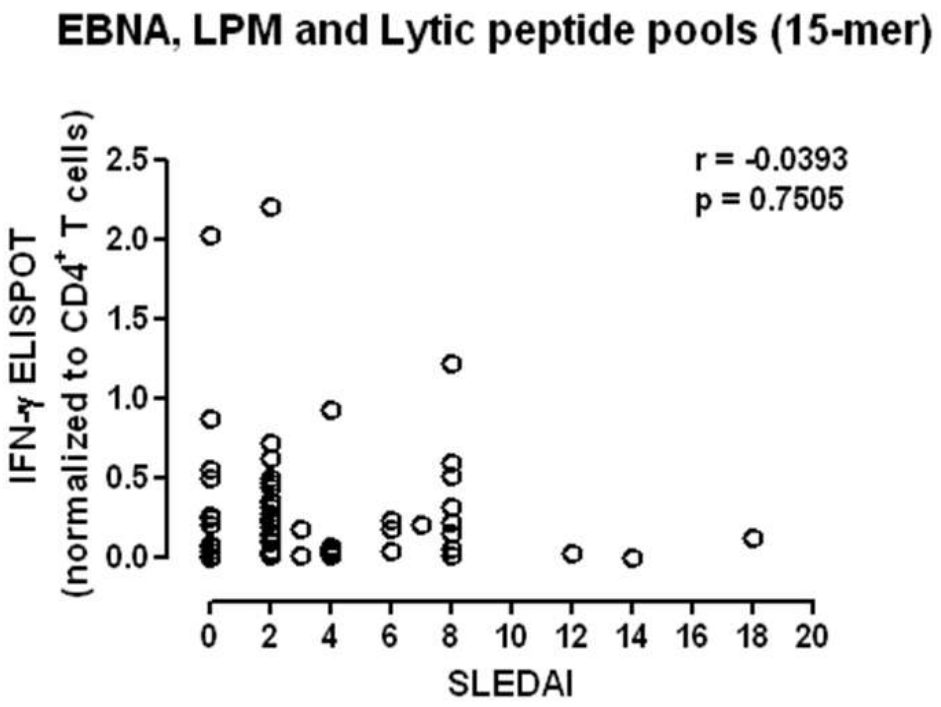


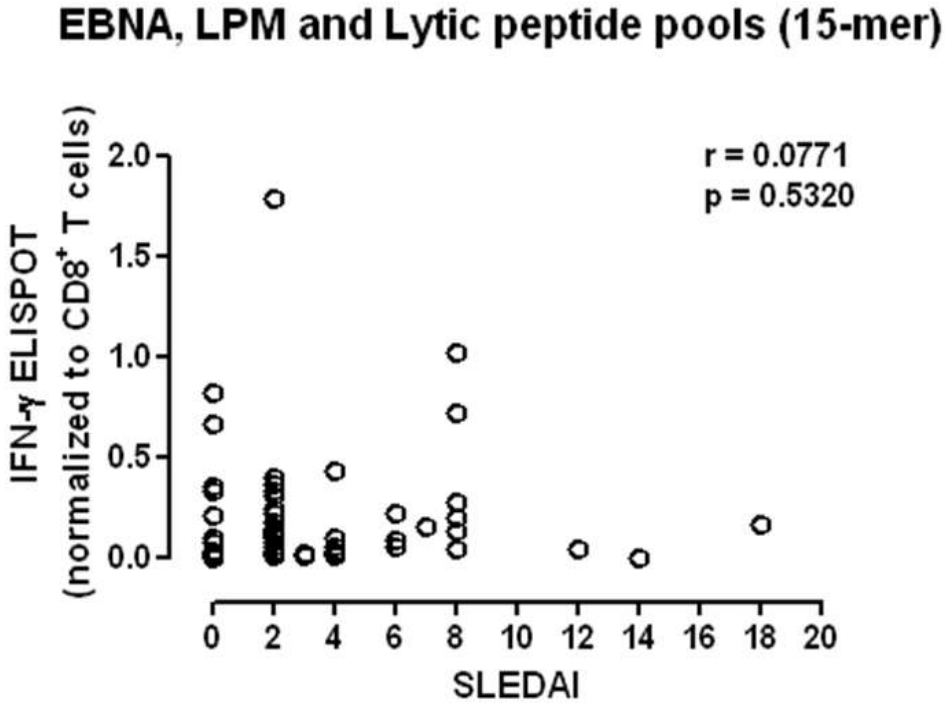


RIDUZIONE RISPOSTA linfociti T CD4 e CD8+ nei confronti dell'EBV

Manuscript in draft

Evaluation of EBV and HCMV-specific T cellular response in SLE patients by using a normalized enzyme- linked immunospot (ELISPOT) assay

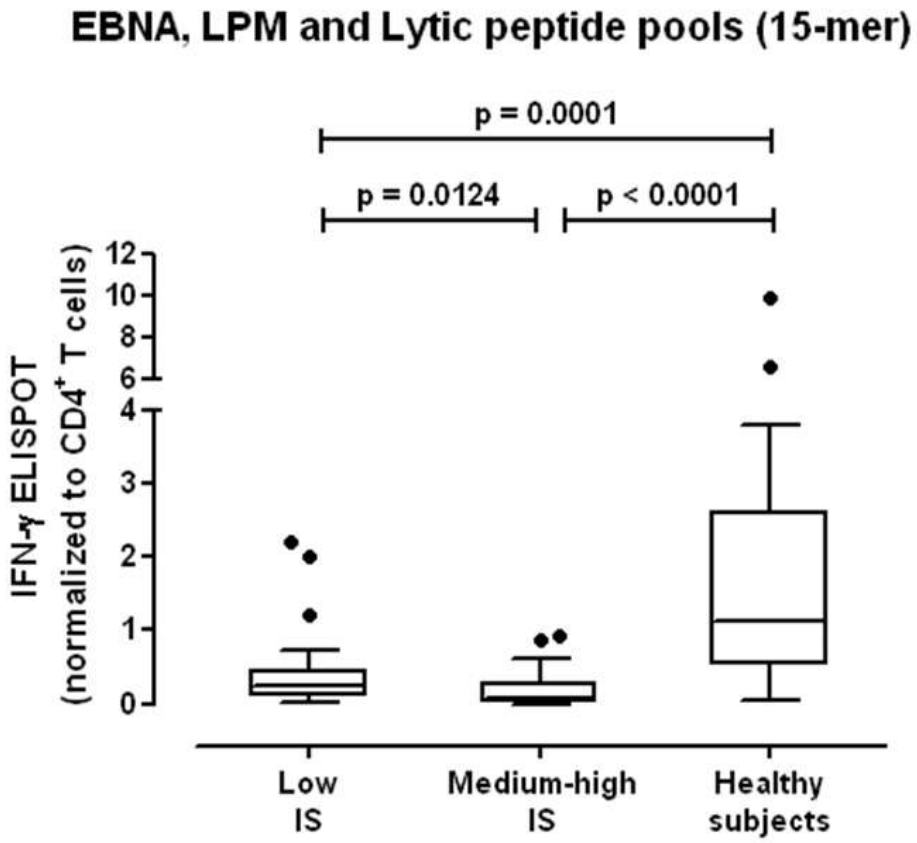


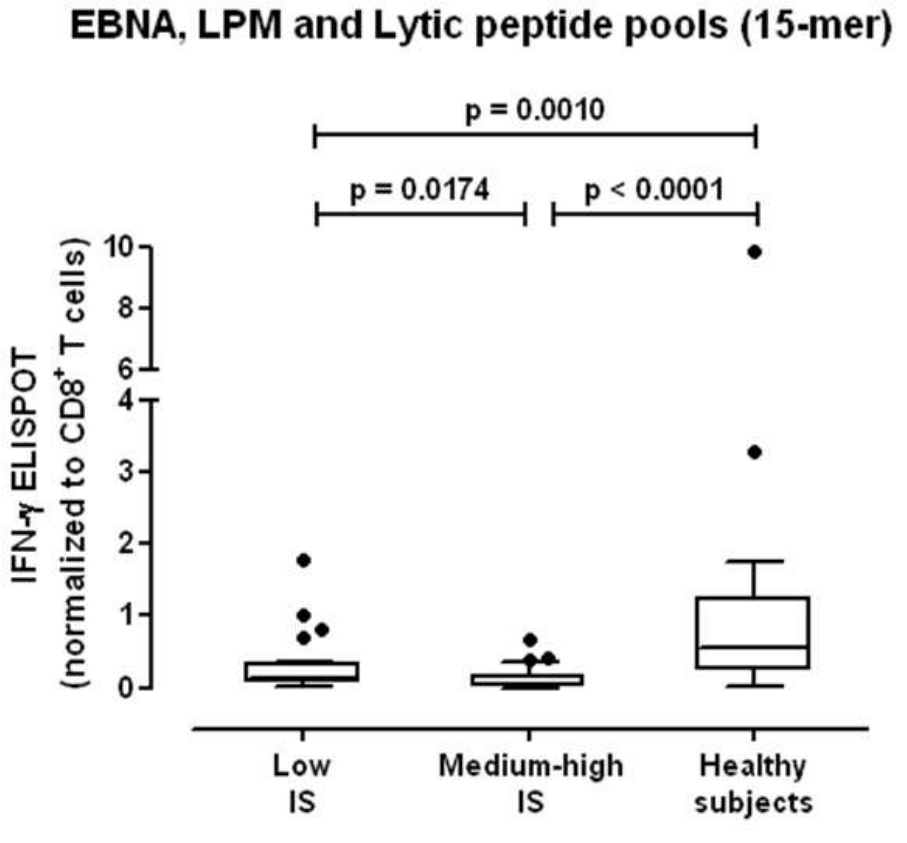


RISPOSTA linfociti T CD4 e CD8+ a EBV non correla con SLEDAI

Manuscript in draft

Evaluation of EBV and HCMV-specific T cellular response in SLE patients by using a normalized enzyme- linked immunospot (ELISPOT) assay





RISPOSTA linfociti T CD4 e CD8+ a EBV influenzata da grado immunosoppressione, ma ridotta sempre rispetto ai controlli sani

Manuscript in draft

Come ci comportiamo se:

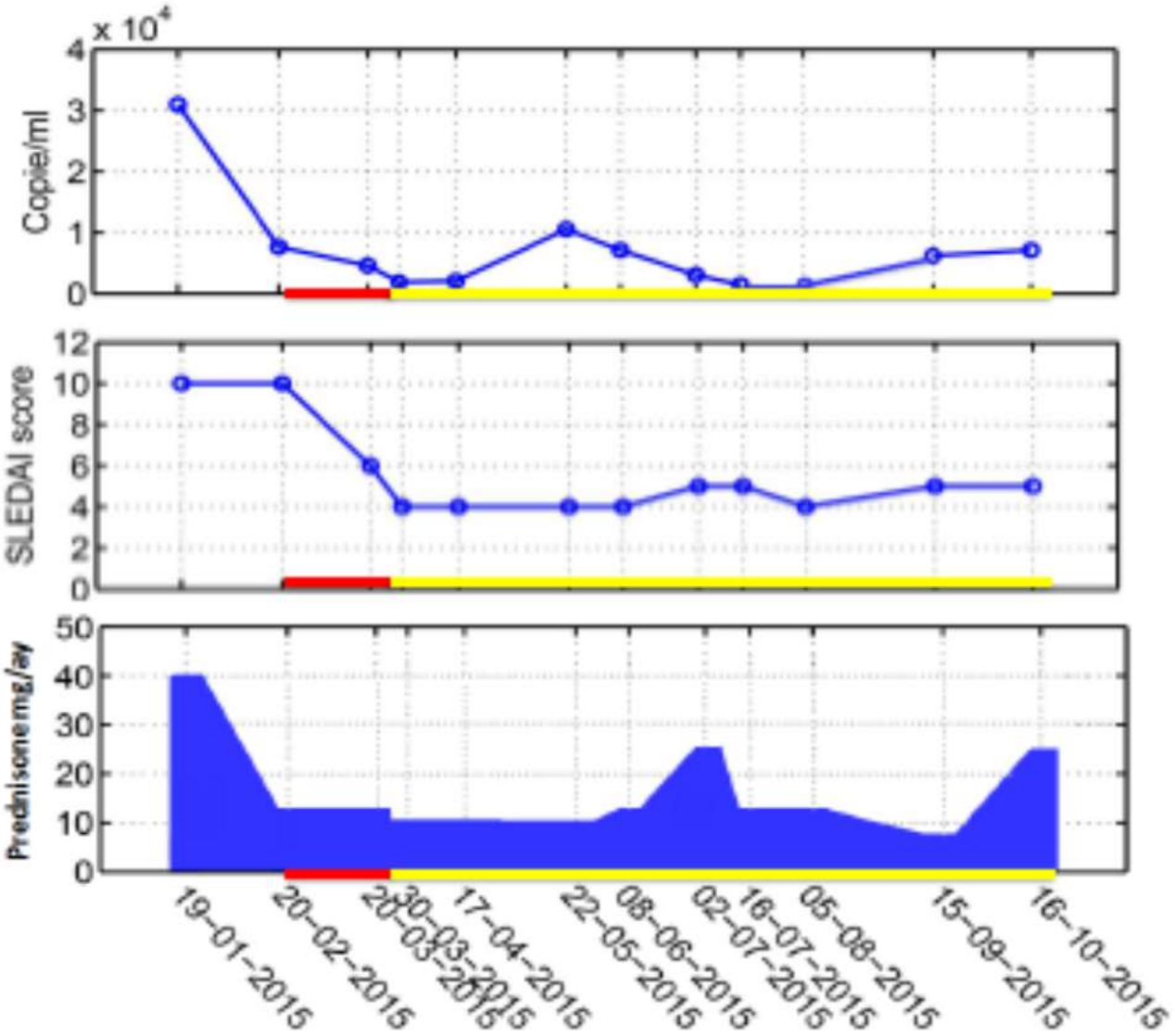
Un paziente ha un'elevata carica di EBV DNA su sangue e un LES attivo?

AZIONE	PRO	CONTRO
Aumentare immunosoppressione	Controllo LES	Aumento rischio infettivo (manifestazioni EBV relate)
Ridurre immunosoppressione	Riduzione del rischio infettivo	Aumento attività di malattia

Esperienza reale: fluttuazione EBV DNAemia con belimumab

Nella **FASE DI INDUZIONE** DI BELIMUMAB abbiamo osservato una riduzione della viremia dell'EBV

Nella **FASE DI MANTENIMENTO** vi è stata una sostanziale stabilità della viremia, tranne un transitorio aumento nelle fase iniziali (dosi piu' distanziate di farmaco) e prima dei flare febbrili



Rituximab in the treatment of **EBV**-positive low grade B-cell lymphoma

Diamantopoulos PT et al, Anticancer Res 2013

"**Rituximab** used in the treatment of EBV-positive low-grade lymphoma is efficient in eradicating the virus from the peripheral blood, a fact with potential implications in the course and prognosis of the disease"

Case report

- M.M., 50 years old female
- 2001: SLE diagnosis (arthritis, ANA +, anti-dsDNA +, fever, subacute cutaneous lupus, anti-Ro +); good disease control with hydroxychloroquine and low dose prednisone
- July 2009: relapse of fever, arthritis and subacute cutaneous lupus; anti-dsDNA (IIF and ELISA) +ve again, C3 and C4 reduction
- Methylprednisolone increased until 24 mg/day P.O., but without fever and other findings improvement; levoxacin trial ineffective

Case report

- December 2009: admission to our Division
- Blood and urine coltures, procalcitonin, urinary legionella and pneumococcal antigen, chest X ray, abdominal ultrasonography, Doppler echocardiography: negatives; anti-dsDNA +ve, C3 and C4 reduced. ESR 56 mm/1h, CRP 2.25 mg/dl (n.v. <0.5). Further increase of Methylprednisolone (40 mg/day), without improvement
- Because of Herpes virus 6 positivity (467,600 copies/ml by Real time PCR), ganciclovir treatment was started (250 mg twice a day)
- After one week of treatment viral load was still high (529,000 copies/ml by Real time PCR); no clinical changes were observed.

What happens?

HHV6 acute infection?

Other active infection?

SLE activity?

Both SLE and infection?

Other possibilities?

What happens?

HHV6 acute infection?

Other active infection?

SLE activity?

Both SLE and infection?

Other possibilities?

Case report

- An high number of viral copies (92680 copies/ml by Real time PCR) was found in the patient's hairs bulb cells

HHV6 INTEGRATION OF THE VIRAL GENOME IN THE HOST CHROMOSOME (CIHHV-6)

- Taking into account signs of disease activity (anti-dsDNA +, C3 and C4 reduction, arthritis, cutaneous finding) methylprednisolone I.V. 1 g/day for 3 consecutive days was started; corticosteroids were then reduced and MTX was started (10 mg/week). Treatment led to disease control.

Cavagna L, et al. Lupus. 2013;22:1087-8.

Biotechnological fiasco drugs in SLE

Systemic lupus erythematosus: Epratuzumab not effective in phase III trials.

Treatment with epratuzumab+ST did not result in improvements in response rates over placebo+ST.

Onuora S, Nat Rev Rheumatol 2016 Sep 22. doi: 10.1038/nrrheum.2016.165.

Efficacy and Safety of Ocrelizumab in Active Proliferative Lupus Nephritis: Results From a Randomized, Double-Blind, Phase III Study

Overall serious infection rates per 100 patient-years were **18.7** (95% CI 12.2, 28.7), **28.8** (95% CI 20.6, 40.3), and **25.1** (95% CI 17.4, 36.1) in the placebo-treated, 400 mg ocrelizumab–treated, and 1,000 mg ocrelizumab–treated groups, respectively

Mysler EF, et al. Arthritis Rheum 2013;65:2368-79