- **Lupus érythémateux disséminé sévère réfractaire**

Le lupus érythémateux systémique (LES), ou lupus érythémateux disséminé, est une maladie systémique protéiforme et spontanément grave caractérisée par la production d'anticorps antinucléaires dirigés en particulier contre l'ADN natif.

En France, l'incidence du LES est estimée à approximativement 3 à 4 nouveaux cas annuels pour 100 000 et la prévalence à 35 pour 100 000.
Le LES survient 85 fois sur 100 chez la femme, généralement en période d'activité ovarienne.
Le LES pédiatrique représenterait 5 à 10 % environ de l'ensemble des LES.

Deux études randomisées en double aveugle versus placebo, EXPLORER (Merill 2010) et LUNAR (Furie 2009, abstract), ne mettent pas en évidence l'efficacité du rituximab dans les formes graves et réfractaires du lupus érythémateux systémique réfractaire à un traitement corticoïde bien conduit et à au moins une ligne d'immunosuppresseur.
Dans ces études, le taux de réponse du groupe traité par rituximab n'est pas significativement supérieur à celui du groupe recevant le placebo et/ou le traitement conventionnel.

Les autres études publiées ne concernent que des études ouvertes, dont l'étude de Terrier 2010 rapportant 136 patients atteints de lupus erythémateux disséminé issus du registre français AIR.

Il est à noter qu'en juillet 2011, le bélimumab a obtenu une AMM pour l'indication : « Benlysta, en association au traitement habituel, est indiqué chez les patients adultes atteints de lupus systémique actif avec présence d'auto-anticorps et activité de la maladie élevée (définie par exemple par la présence d'anticorps anti-ADN natif et un complément bas) malgré un traitement standard ».

Effet du rituximab dans le lupus érythémateux disséminé

Auteurs	Type d'étude	Posologie	Suivi	Critères d'évaluation	Résultats
Merill (2010) Explorer	**Randomisée double-aveugle versus placebo : N = 257 patients (16-75 ans)** atteints de lupus modéré à sévère traités par immunosuppresseurs **(Phase III)**	Rituximab : 1g x2 à 2 semaines d'intervalle à J1, J15, J168, J 182 (n=169) ou placebo (n=88) + prednisone : 0.5 mg/kg ou 0.75 mg/kg ou 1 mg/kg + immunosupresseurs (azathioprine : 100-250 mg/j ou MMF : 1-4 g/j ou méthotrexate : 7.5-27.5 mg/sem)	1 an	BILAG : 1x /mois Lupus QdV en fonction du SF-36 + douleur + fatigue Tolérance	<u>Réponse majeure</u> : BiLAG C ou D ou E pour tous les organes à la S24 sans poussée sévère et maintien de cette réponse sans poussée modérée ou sévère dans de nouvelles régions <u>Réponse partielle</u> : - BILAG C, D ou E à S24 et maintien de cette réponse sans poussée pdt 16 sem - Atteindre un maximum de 2 scores de BILAG B à S24 sans atteindre un score BILAG A ou B jusqu'à la S52 - Atteindre un maximum de 2 scores de BILAG B à S24 sans développer de score BILAG A ou B dans de nouvelles régions jusqu'à la S52 si score de BILAG de base : 1A + ≥ 2B ou ≥ 2A ou ≥ 4B Réponse majeure à S52 : **NS** Réponse partielle : **NS** Réponse totale : **NS** <u>Analyse en sous groupe</u> : - sous-groupe des africains/ hispaniques : Réponse **: S (p = 0.0408)** % de non-répondeurs plus élevé dans le gpe placebo de ce sous-groupe de patients versus autres groupes placebo.

Auteurs	Type d'étude	Posologie	Suivi	Critères d'évaluation	Résultats
					Critères secondaires : **NS** Effets indésirables : **NS** (placebo : 36.4%, traités : 37.9%) Gp traité : Troubles neurologiques (14.2%), troubles gastro-intestinaux (14.2%) et généraux (10.7%)
Furie Abstract (2009)	**Randomisée double-aveugle versus placebo N = 144** patients adultes atteints de néphrite lupique **(Phase III) : Lunar study**	Rituximab (n=72) 1 g à J1, J15, J168 et J182 + MMF : 3 g/j + corticostéroïdes Pla (n=72) + MMF : 3 g/j + corticostéroïdes		Critères primaires : % de patients avec une RC ou une RP à S52	RC et RP : **NS** anti-ds DNA : ↓**S (p = 0.007)** taux C3 : ↑**S (p = 0.025)** Population noire et hispanique : meilleure réponse mais **NS** Effets indésirables : **NS**
Terrier (2010) Registre français AIR (autoimmunity registry)	**Prospective : N = 136** patients atteints de SLE dont n = 42 : néphrite lupique, n = 16 : AITP n = 14 : AHAI	Rituximab + corticostéroïdes (n = 125) ou rituximab + immunosuppresseurs (n = 71) ou rituximab + hydroxychloroquine (n = 72)		Amélioration clinique ≥ 50% (RP) ou disparition des symptômes cliniques (RC) Activité de la maladie par SLEDAI Effets indésirables	Réponse globale (SLEDAI): n = 80/113 (71%) Réponse clinique : n = 87/113 (77%) Rituximab en monothérapie : tendance vers une meilleure réponse Amélioration : Articulaire : 72% Cutanée : 70% Rénale : 74% : RC : 45% ; RP : 29% Hématologique : 88% Doses de corticoïdes : ↓ Rechute parmi les répondeurs : 41% Après un 2ème traitement par rituximab : réponse : 91% Effets indésirables : - infections sévères : 9% (6.6 pour 100 patients- années) - décès : 5 (infections sévères (n = 3) et maladie auto-immune réfractaire (n = 2))
Lu (2009)	**Prospective : N = 45** patients (âge moyen : 32.8 ans) réfractaires aux traitements standards	Rituximab : 1 g + cyclophosphamide : 750 mg + méthylprednisolone : 100-250 mg	39.6 mois en moyenne	Rémission Tolérance	A M6 (1 cycle de BCDT) Rémission : n = 19/45: 42% RP : n = 21/45 (47%) Non-répondeurs : n = 2 Score BILAG : ↓ 12 à 5 (**p < 0.0001**) Titre des anti-ds DNA : ↓ **S**(**p < 0.0001**) 106 à 42 UI/ml taux C3 de 0.81 à 0.95 mg/l : ↑**S** (**p < 0.02**) Effets indésirables graves : n = 5 décès : n = 2

Auteurs	Type d'étude	Posologie	Suivi	Critères d'évaluation	Résultats
Catapano (2010)	**Prospective : N = 31** patients atteints de SLE réfractaire aux traitements conventionnels immunosuppresseurs ou en rechute néphrite lupique : n = 11	Rituximab n = 16 : 375 mg/m² pdt 4 sem n = 15 : 1 g x 2	30 mois	Rémission complète ou partielle Déplétion en cellules B	Réponse globale : 27/ 31 (87%): RC : n = 17 RP : n = 10 Réponse rénale : n = 10/11 RC : n = 4 RP : n = 6 Déplétion en cellule B à S4 : 97% (30 /31) Rechute après une médiane de 11 mois : n = 18/27 (67%) Présence de cellules B circulantes : n = 10 Absence de cellules B circulantes : n = 8 2ème traitement par rituximab efficace : réponse : n = 20/22 (90%) Effets indésirables Infections : 8/31 : 26% Neutropénie : n = 1 Décès : n = 3
Leandro 2005	**Ouverte : N =24**	6 premiers patients: Rituximab : 500 mg +cyclophosphamide 750 mg +prednisolone PO 60 mgx2/j pdt 5 j X 2 à 2 semaines d'intervalle: 18 patients suivants: Rituximab : 1 g + 750 mg cyclophosphamide + prednisolone IV 250 mg X 2 à 2 semaines d'intervalle	Suivi moyen: 23 mois 6 mois pour 19 patients	Score BILAG C3 sérique Ac anti-DNA	score BILAG : Amélioration significative à 6 mois (p<0.00001), C3 sériques : ↑ **S (p<0.0005)** Ac anti-ds DNA : ↓ **S (p<0.002)** prednisolone ↓ de 13.8 à 10 mg/j. Effets indésirables Pancytopénie n=1, décès par pancardite n=1, pas d'infections opportunistes graves
Vigna-Perez 2006	**Ouverte : N =22**	Rituximab : 0.5 à 1 g à J1 et J15 associé au tt immuno-suppresseur	3 mois	Réponse complète (RC) : créatininémie nale +sédiment urinaire inactif+protéinurie<500mg/24h Rémission partielle (RP) : >40%amélioration des paramètres rénaux	- RC : 5/22 (23%) - RP : 7/22 (32%) - SLEDAI ↓ **S** dans 90% des cas - Protéinurie : ↓ **S** - Clairance créatinine ↑ (72% des cas) mais **NS** Effets indésirables : Décès par histoplasmose invasive n=1.

Auteurs	Type d'étude	Posologie	Suivi	Critères d'évaluation	Résultats
Melander (2009)	**Prospective: N = 20** patients avec une néphrite lupique classe IV : n = 15 classe V : n = 5 n = 12 patients réfractaires au traitement standard n = 6 patients ayant eu une rechute n = 2 patients en traitement de 1ère ligne	Rituximab : 375 mg/m²/ sem pdt 4 sem + cyclophosphamide (n=3) 10 patients ont reçu de nouvelles injections de rituximab en traitement d'entretien	22 mois	Rémission Tolérance	A M22 : Rémission clinique globale : 12/20 : 60% RC : n = 7 RP : n = 5 Réponse < 6 mois : n = 6 Réponse à 1 an : n = 5 Réponse à M26 : n = 1 Réponse chez les patients atteints de néphrite lupique proliférante : n = 10 (66%) RC : n = 5 RP : n = 5 Echec : n = 5 Rechute à M9 : n = 1 (ce patient a ensuite répondu à une nouvelle injection de rituximab) Glomérulonéphrite progressive ne répondant pas au rituximab : n = 3 Effets indésirables : - infections : n = 5 - neutropénie modérée : n = 4 - encéphalopathie postérieure réversible : n = 2 - décès : n = 1
Pepper (2009)	**Prospective : N = 18** patients avec néphrite lupique (classe III/IV/V)	Rituximab : - 1 g x2 (J1 et J15) (n=10) - 1 g x2 (J1 et J15) + méthylpredniso lone IV : 500 mg x 2 (J1 et J15) (n=8) + corticoïdes + MMF : 1 g/j	1 an	Rémission complète ou partielle Protéinurie Sérum albumine CRP	RC : normalisation de la créatinine sérique, sérum albumine et protéinurie minimale définie par CRP < 50 (50 mg/24h) RP : ≥ 50% d'amélioration de la protéinurie + normalisation du taux de sérum albumine. RC ou RP : n = 14/18 (78%) : avec une réponse maintenue à 1 an : (12/18) : 67% RC : 6/ 18 (33.3 %) RP : 6/18 Rechute : n = 2 Non-répondeurs : n = 4 Protéinurie : ↓ CRP : ↓ **S (p = 0.004)** Sérum albumine : ↑ **S (p = 0.001)** Traitement par corticoïdes : n = 6 patients : arrêt du traitement n = 6 : ↓ des doses n = 6 : maintien de la dose (10 mg)
Looney 2004	**Ouverte, prospective** **N =17**	Rituximab : -1 inj 100 mg/m² - ou 1 inj 375 mg/m² - ou 375 mg/m²/sem x4 doses	12 mois	Score SLAM[4] Taux de lymphocytes CD19+	Amélioration significative du score SLAM à 2 et 3 mois (p=0.0016 ; p=0.0022), réponse maintenue à 12 mois Effets indésirables : Bronchospasme lors injection n=1, AIT n=1, zona n=1, fasciite nécrosante n=1 (déficit immunitaire congénital)

Auteurs	Type d'étude	Posologie	Suivi	Critères d'évaluation	Résultats
Boletis (2009)	**Prospective : N = 10** femmes en rechute de néphrite lupique et en traitement de maintien par MMF ou azathioprine	Rituximab : 375 mg/m² / sem pdt 4 sem + MMF(2g/j) + prednisolone (0.5 mg/kg/j pdt 4 sem)	38 mois	Rémission Tolérance	RP (>50% d'amélioration des paramètres rénaux) : n = 8 RP en 3.5 mois (médiane) puis RC : n = 7 : . ↑ des taux de complément sérique, . ↓ anti-dsDNA, . Créat sérique et taux d'albumine sérique : normaux . ↓ des doses de corticoïdes Rémission complète maintenue pdt 38 mois en moyenne : n = 6 Bonne tolérance
Sfikakis 2005	**Ouverte Prospective n=10**	Rituximab : 375 mg/m²/sem x4 doses + prednisolone	12 mois	Rémission complète (RC): créatininémie nale+ albuminémie nale + sédiment urinaire inactif + protéinurie des 24h<500mg Rémission partielle (RP) : amélioration de >50% des paramètres rénaux anormaux à l'inclusion	RC: n=5/10 Maintien de la rémission complète à 12 mois chez 4 patients RP: n=8/10 Effets indésirables : Réaction hypersensibilité n=1, infections respiratoires hautes non graves n=3, méningite à pneumocoque n=1
Marks 2005	**Ouverte : N =7 enfants** de 7 à 16 ans - atteinte muti-systémique réfractaire et menaçant le pronostic vital : n=4	Rituximab : 750 mg/m² x2 doses +cyclophosphamide +corticothérapie orale	1 an	Symptômes cliniques Score BILAG[2]	Amélioration clinique : **n=7/7** - Amélioration significative du score BILAG de 22 (14-37) à l'inclusion à 6 (4-11) **(p=0.002)** - Amélioration fonction rénale : **NS** mais ↓ créatinémie (n= 2 avec atteinte rénale lupique grave (de 273 et 195 µmol/l à 66 et 61 µmol/l après tt)
Willems 2006	**Ouverte : N =8 enfants**	Rituximab : 350-450 mg/m² x2-12 doses +corticothérapie +/-immuno-suppresseur (n=6)	13.2 mois	- Rémission néphrite lupique ou cytopénie auto-immune	Rémission : 8/11 **(73%)** EI graves : n=5
Leandro 2002	**Ouverte : N =6**	Rituximab : 500 mg/sem x2 +cyclophosphamide 750 mg/sem x2 +corticothérapie haute dose	6 mois	Score BILAG Symptômes cliniques (asthénie, arthralgies, épanchements séreux)	Amélioration du score BILAG de 14 (9-27) à 6 (3-8) à 6 mois : n=5/6 (83%) - Pas d'infection grave

Auteurs	Type d'étude	Posologie	Suivi	Critères d'évaluation	Résultats
Gottenberg 2005	**Série de cas** **N =13** **Rétrospective**	Rituximab : 375 mg/m²/sem x1-4 doses	8 mois	SLEDAI RC : SLEDAI entre 0 et 2 RP : ↓SLEDAI de 50% :	RC+RP : n=9/13 (69%) RC : 7/13 (54%) RP : 2/13 Décès : n=2 ↓ corticothérapie de 9.5mg/jour Effets indésirables Neutropénie n=2, thrombose veineuse n=1, embolie pulmonaire n=1
Ramos Casal (2010)	**Rétrospective** **N = 106** atteints de néphrite lupique issus de 7 études observationnelles de 2005 à 2009 Age moyen : 31.4 ans	Rituximab : 375 mg/m² x 4 (n=57) ou 500-1000 mg/m² x2 ou 1 g/m² x 2 (n = 59) - en 1ère ligne (n=17) - chez des patients réfractaires (n=52) - en cas de poussée (n=37)		Réponse : Complète : - Créat serique et taux de sérum albumine normaux - Albumine urinaire < 0.5g Réponse partielle : > 50% amélioration et normalisation de tous les paramètres rénaux Tolérance	RC ou RP : Néphrite lupique : n = 73 (69%) . RC : n = 33, . RP : n = 35, Réponse en fonction du type de néphrite lupique a été évaluée chez 79 patients : . Type III : n = 8 (80%) avec RC : 60% . Type IV : n = 26 (67%) avec RC : 39% . Type V : n = 4 (57%) . Autre : n= 18 (78%) Non-répondeurs : jeune âge, race noire, absence de déplétion des CD19+ Effets indésirables : n = 42 (40%) . infections (n = 30) dont n = 4 sévères . neutropénie : n = 5 . encéphalopathie postérieure réversible : n = 2 . décès : n = 3
Garcia-Carrasco (2010)	**Rétrospective (Analyse longitudinale)** **N = 52** patients (âge moyen : 36 ans) hispaniques réfractaires aux traitements conventionnels n = 13 : néphrite lupique n = 8 : thrombocytopénie n = 3 : leucocytopénie n = 25 : atteinte musculo-	Rituximab : 1 g + corticoïdes : méthylprednisolone J1 et J 15 + immunosuppresseurs : cyclophosphamide, MMF, azathioprine	6 mois	Activité de la maladie par le MEXSLEDAI Fonction rénale : clairance de la créatinine, hématurie, protéinurie	A M 6 : Amélioration clinique : ↓ **S** MEXSLEDAI : **p < 0.0001** Patients atteints de néphrite lupique : RC rénale : n = 5/13 (38.4%) RP : n = 5/13 Amélioration significative des patients atteints de thrombocytopénie : n = 6/8 (87%) [plaq] : ↑ **S : p = 0.012** ↓ des corticoïdes de 50% Rémission de l'arthrite : n = 19/25 patients avec une atteinte musculo-squelettique sévère Patients leucopéniques : ↑ des leucocytes (x2) Disparition des lésions : 1/ 3 des patients avec des lésions de la peau ↓ des corticoïdes

Auteurs	Type d'étude	Posologie	Suivi	Critères d'évaluation	Résultats
	squelettique n = 3 : lésions de la peau				
Reynolds (2009)	**Rétrospective : N = 11 patients** (42 ans en moyenne) SLE réfractaire au traitement standard	Rituximab : 750 mg ou 1 g x2 à 2 sem d'intervalle (n=8) + cyclophosphamide : 500 mg - 750 mg (n=7/8) + methylprednisolone : 250-500 mg (n=6/8) Rituximab seul (n=2) Rituximab (500 mg) + cyclophosphamide (750 mg) (n=1)		- BILAG - Complément sérique - Réduction de la dose des corticoïdes - AC anti-dsDNA - Cellules B - Fonction pulmonaire - Tolérance	A M6 : Réponse : n = 10/11 (↓ **BILAG de 7.5 : p = 0.007**) Normalisation du taux des compléments sériques : ↑C3 : **p = 0.008 ;** ↑C4 **: p = 0.018**) ↓ des doses des corticoïdes : ↓ 15 mg/j : **p = 0.036** Arrêt des immunosuppresseurs : n = 9/10 des répondeurs : AC anti-ds DNA : **NS** ↓ cellules B Pas d'infection grave
Lateef (2010)	**Rétrospective : N = 10** adultes (âge moyen : 28 ans) avec SLE réfractaire au traitement standard	Rituximab : 375 mg/m² x2 + Cyclophosphamide : 500 mg espacé de 2 sem + corticoïdes		- BILAG - Réponse rénale complète ou partielle - Réponse hémato : [plaq] > 100 G/L - Temps d'hospitalisation - Tolérance	- Scores BILAG : amélioration : 9/10 : **p < 0.05** - protéines urinaires chez les patients atteints de néphrites lupiques : ↓ - Normalisation des plaquettes : n = 2/3 patients atteints de thrombocytopénies - Déplétion des cellules B : durée médiane : 6 mois - Rechute : n = 2, puis réponse avec un 2ème traitement - Temps d'hospitalisation : ↓
Edelbauer 2005	**Cas clinique N =1** (14 ans)	Rituximab : 375 mg/m²/sem x6 doses +MMF+prednisone puis Rituximab en entretien/3 mois	1 an	SLEDAI[3] Créatininémie, protéinurie, hématurie	- Persistance hématurie et cylindres urinaires - Score SLEDAI ↓de 31 à 14 après 9 doses RTX - Créatininémie normale - Protéinurie ↓ Pas d'EI rapporté

SLE : systemic lupus erythematosus
RC : rémission complète
RP : rémission partielle
CRP : protein creatinine ratio
BCDT : B cell depletion therapy
AITP : thrombocytopénie auto-immune
BILAG: British Isles Lupus Assessment Group
MEXSLEDAI : SLEDAI de la population mexicaine
AHAI anémie hémolytique automimmune
SLEDAI: SLE disease activity index
score SLAM: Systemic Lupus Activity Measure

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Résumés -Abstracts

Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial.
Merrill JT, Neuwelt CM, Wallace DJ, Shanahan JC, Latinis KM, Oates JC, Utset TO, Gordon C, Isenberg DA, Hsieh HJ, Zhang D, Brunetta PG. Arthritis Rheum. 2010 Jan;62(1):222-33.

OBJECTIVE: B cells are likely to contribute to the pathogenesis of systemic lupus erythematosus (SLE), and rituximab induces depletion of B cells. The Exploratory Phase II/III SLE Evaluation of Rituximab (EXPLORER) trial tested the efficacy and safety of rituximab versus placebo in patients with moderately-to-severely active extrarenal SLE. METHODS: Patients entered with >or=1 British Isles Lupus Assessment Group (BILAG) A score or >or=2 BILAG B scores despite background immunosuppressant therapy, which was continued during the trial. Prednisone was added and subsequently tapered. Patients were randomized at a ratio of 2:1 to receive rituximab (1,000 mg) or placebo on days 1, 15, 168, and 182. RESULTS: In the intent-to-treat analysis of 257 patients, background treatment was evenly distributed among azathioprine, mycophenolate mofetil, and methotrexate. Fifty-three percent of the patients had >or=1 BILAG A score at entry, and 57% of the patients were categorized as being steroid dependent. No differences were observed between placebo and rituximab in the primary and secondary efficacy end points, including the BILAG-defined response, in terms of both area under the curve and landmark analyses. A beneficial effect of rituximab on the primary end point was observed in the African American and Hispanic subgroups. Safety and tolerability were similar in patients receiving placebo and those receiving rituximab. CONCLUSION: The EXPLORER trial enrolled patients with moderately-to-severely active SLE and used aggressive background treatment and sensitive cutoffs for nonresponse. No differences were noted between placebo and rituximab in the primary and secondary end points. Further evaluation of patient subsets, biomarkers, and exploratory outcome models may improve the design of future SLE clinical trials.

Efficacy and Safety of Rituximab in Subjects with Active Proliferative Lupus Nephritis (LN): Results From the Randomized, Double-Blind Phase III LUNAR Study
Furie R, Looney R. J, Rovin B., Latinis KM., Appel G., Sanchez-Guerrero J, Fervenza, F.C. Arthritis & Rheumatism, Volume 60, October 2009 Abstract
Supplement The 2009 ACR/ARHP Annual Scientific Meeting, Philadelphia October 16-21, 2009.

Purpose: Small, uncontrolled LN studies have suggested that RTX may be efficacious. The efficacy and safety of RTX compared to placebo (PLA) added on to background therapy of mycophenolate mofetil (MMF) and corticosteroids in pts with proliferative LN was studied.
Methods: Pts with class III/IV LN and urine protein to creatinine ratio (UPCR) >1 were randomized 1:1 to receive RTX (1000mg) or PLA on days 1, 15, 168, and 182. Primary endpoint (EPS) was % pts with complete (CRR) or partial renal responses (PRR) at Wk 52 and was analyzed by a stratified Wilcoxon rank sum test.
Results: 72 pts were randomized to each arm and were similar at baseline (BL). Overall mean age at entry was ~30 yrs, ~90% were female, 28% were Black, 36% Hispanic, 31% White, and 67% had class IV LN. BL mean UPCR was 4.0 ±2.8 and serum creatinine was 1.0 ±0.5 mg/dL Mean daily MMF dose was 2.4±0.63g in PLA and 2.7±0.41g in RTX. There were no statistically significant differences in the primary or clinical secondary EPS. Blacks and Hispanics randomized to RTX had greater responses compared to PLA than Whites, but statistical significance was not achieved. RTX had a greater effect on levels of anti-dsDNA and complement at Wk 52. Peripheral CD19+ B cells were depleted in all RTX pts and maintained in most pts until Wk 52. Serious adverse events (SAEs) and infectious SAEs were similar between groups. Neutropenia (1 vs 4), leukopenia (3 vs 9), and hypotension (3 vs 9) occurred more frequently in RTX. Two deaths (sepsis and pneumonitis) occurred in the RTX group.
Conclusion: To date, LUNAR is the largest randomized, placebo-controlled trial to evaluate RTX as an intervention in LN. Although there were numerically more responders in the RTX group (57% vs 46%), the study did not show a statistically significant difference in primary or clinical secondary EPS. RTX had a significantly greater effect on levels of anti-dsDNA and complement, although the clinical significance of this is unclear. AEs and SAEs were similar in frequency between groups, with no new or unexpected safety signals.

Table. Efficacy EPS and Safety

	PLA (N=72) N (%)	RTX (N=72) N (%)	p-value*
Primary			
CRR	22 (30.6)	19 (26.4)	0.55

	PLA (N=72) N (%)	RTX (N=72) N (%)	p-value*
PRR	11 (15.3)	22 (30.6)	
Key Secondary			
Pts with BL UPCR>3 to UPCR<1	53.7	47.4	0.51
% change from BL in anti-dsDNA	50	69	<0.01
Mean Change from BL in C3 (mg/dL)	25.9	37.5	<0.03
Exploratory			
Pts with BILAG Renal Domain Score C at Wk52	28 (38.9)	39 (54.2)	0.07
Overall response (CRR+PRR)	33 (45.8)	41 (56.9)	0.18
Black	9/20 (45)	14/20 (70)	0.20
Hispanic	11/23 (48)	16/29 (55)	0.78
White	13/26 (50)	10/19 (53)	1.00
Pts with new immunosuppressant prior to Wk52	8 (11.1)	1 (1.4)	0.03
Safety	(N=71)	(N=73)	
SAE	25 (35.2)	22 (30.1)	
Infusion-related SAE	2 (2.8)	1 (1.4)	
Infection AE	61 (85.9)	61 (83.6)	
Infection SAE	12 (16.9)	12 (16.4)	
HACA+	4 (5.6)	8 (11.1)	
Deaths	0 (0)	2 (2.7)	
*P-values are 2-sided and not adjusted for multiplicity			

Safety and efficacy of rituximab in systemic lupus erythematosus: Results from 136 patients from the French AIR registry.
Terrier B, Amoura Z, Ravaud P, Hachulla E, Jouenne R, Combe B, Bonnet C, Cacoub P, Cantagrel A, De Bandt M, Fain O, Fautrel B, Gaudin P, Godeau B, Harlé J, Hot A, Kahn J, Lambotte O, Larroche C, Léone J, Meyer O, Prades BP, Pertuiset E, Quartier P, Schaerverbeke T, Sibilia J, Somogyi A, Soubrier M, Vignon E, Bader-Meunier B, Mariette X, Gottenberg JE; for the Club Rhumatismes et Inflammation. Arthritis Rheum. 2010 May 5.

BACKGROUND.: A number of open-label studies have suggested the potential benefit of rituximab (RTX) in systemic lupus erythematosus (SLE). However, two recent randomized controlled trials (RCTs) failed to meet their primary endpoints. OBJECTIVE.: To evaluate the safety and efficacy of RTX in SLE in off-trial real-life patients. METHODS.: Prospective data from the French AutoImmunity and Rituximab (AIR) registry, which includes data on patients with autoimmune disorders treated with RTX, were analyzed. RESULTS.: 136 patients received treatment for SLE. Mean baseline SLE Disease Activity Index was 11.3+/-8.3. Severe infections were noted in 12 patients (9%), corresponding to a rate of 6.6/100 patient-years. Severe infections occurred within the first 3 months after the last RTX infusion. Five patients died because of severe infection (n=3) and refractory autoimmune disease (n=2). Overall response was observed in 80/113 (71%) patients. Efficacy did not significantly differ between patients treated with RTX in monotherapy and those with concomitant immunosuppressive therapy, who had a higher baseline disease activity. Articular, cutaneous, renal and hematological improvements were noted in 72%, 70%, 74% and 88% of patients, respectively. Among responders, 41% experienced a relapse, with a response in 91% after retreatment with RTX. CONCLUSION.: Data from the AIR registry show a satisfactory tolerance profile and clinical efficacy of RTX in real-life patients with SLE. The contrasting results with recent RCTs results leave open the question of the therapeutic interest of RTX in SLE. Additional controlled studies with new designs are required to define the place of RTX in the therapeutic arsenal of SLE.

A retrospective seven-year analysis of the use of B cell depletion therapy in systemic lupus erythematosus at University College London Hospital: the first fifty patients.
Lu TY, Ng KP, Cambridge G, Leandro MJ, Edwards JC, Ehrenstein M, Isenberg DA. Arthritis Rheum. 2009 Apr 15;61(4):482-7.

OBJECTIVE: To describe the 6-month clinical outcome and the long-term safety profile of B cell depletion therapy (BCDT) in 50 patients with active systemic lupus erythematosus (SLE), who were nonresponsive or poorly responsive to conventional immunosuppression. METHODS: All except 4 of 50 patients with active SLE received 1 gm of rituximab, 750 mg of cyclophosphamide, and 100-250 mg of methylprednisolone, administered on 2 occasions 2 weeks apart, to achieve B cell depletion. Clinical outcome was assessed using the British Isles Lupus Assessment Group (BILAG) activity index and serial serologic measurements of disease activity. Remission was defined as a change from a BILAG A or B score to a C or D score in every organ system. Partial remission was a change from a BILAG A or B score to a C or D score in at least 1 system, but with the persistence of 1 score of A or B in another system. No improvement was defined as a BILAG A or B score that remained unchanged after

treatment. RESULTS: Of the 45 patients available for followup at 6 months, 19 patients (42%) achieved remission, and 21 patients (47%) reached partial remission after 1 cycle of BCDT (mean followup 39.6 months). BCDT resulted in a decrease in median global BILAG scores from 12 to 5 (P < 0.0001) and median anti-double-stranded DNA antibody titers from 106 to 42 IU/ml (P < 0.0001), and an increase in the median C3 level from 0.81 to 0.95 mg/liter (P < 0.02) at 6 months. Five serious adverse events were observed. CONCLUSION: BCDT is an effective treatment for patients with active SLE whose disease has failed to respond to standard immunosuppressive therapy. Although the safety profile of BCDT is favorable, ongoing monitoring is required.

Long-term efficacy and safety of rituximab in refractory and relapsing systemic lupus erythematosus.
Catapano F, Chaudhry AN, Jones RB, Smith KG, Jayne DW. Nephrol Dial Transplant. 2010 May 11.

BACKGROUND: Systemic lupus erythematosus is a relapsing autoimmune disease. Conventional therapy increases the risk of infection and malignancies; furthermore, a minority of patients suffer from refractory disease. B-cell depletion with the chimeric +AFw-anti-CD20 monoclonal antibody, rituximab, is an alternative therapy for relapsing and refractory systemic lupus erythematosus. We sought to assess the long-term efficacy and safety of rituximab in this patient subgroup. METHODS: Thirty-one sequential patients with relapsing or refractory systemic lupus erythematosus, 11 of whom had active lupus nephritis, received rituximab [either 375 mg/m(2)/week x 4 (n = 16) or 1000 mg x 2 (n = 15)]. The median follow-up was 30 months. RESULTS: Thirty of 31 (97%) patients had depleted peripheral B cells. Twenty-seven of 31 (87%) patients achieved remission (17 complete, 10 partial). Renal response occurred in 10/11 patients (4 complete, 6 partial) with active glomerulonephritis. Clinical improvement was reflected by reductions of disease activity, proteinuria and daily prednisolone dose. Eighteen of 27 (67%) patients relapsed after a median of 11 months. Relapses occurred on or after the return of circulating B cells in 10 but in the absence of B-cell return in 8. Re-treatment with rituximab was effective. Infusion reactions were common (18/31; 58%), and infections occurred in 8/31 (26%) patients. CONCLUSIONS: Rituximab had a high rate of efficacy in relapsing or refractory systemic lupus erythematosus with or without renal involvement. Although relapse was common, it responded to re-treatment. The contribution of rituximab to infection risk was uncertain in view of the complex disease course and concomitant therapy of the patients studied.

B-cell depletion in the treatment of patients with systemic lupus erythematosus: a longitudinal analysis of 24 patients.
Leandro MJ, Cambridge G, Edwards JC, Ehrenstein MR, Isenberg DA. Rheumatology (Oxford). 2005 Dec;44(12):1542-5.

OBJECTIVES: To assess the clinical and basic serological consequences of B-cell depletion with rituximab in the treatment of patients with systemic lupus erythematosus (SLE) who have failed conventional immunosuppression.
METHODS: An open study of 24 patients with severe SLE followed for a minimum of 3 months is reported. In the majority of patients (19 out of 24), 6 months follow-up data are described. Disease activity in these patients was assessed every 1-2 months using the British Isles Lupus Assessment Group (BILAG) system and estimates of anti-double-stranded DNA antibodies and serum C3 levels. During the follow-up period, significant side-effects were sought and the reduction in oral prednisolone was recorded. It was our general practice to stop concomitant immunosuppression (e.g. azathioprine, mycophenolate) when B-cell depletion was given (in most cases in the form of two 1 g intravenous infusions of rituximab 2 weeks apart accompanied by two 750 mg intravenous cyclophosphamide infusions and two methylprednisolone infusions of 250 mg each).
RESULTS: Twenty-two patients were female and two male. At the time of B-cell depletion, the mean age was 28.9 yr (range 17-49) and the mean disease duration was 7.9 yr (range 1-18). The global BILAG score (P < 0.00001), serum C3 (P < 0.0005) and double-stranded DNA binding (P < 0.002) all improved from the time of B-cell depletion to 6 months after this treatment. Only one patient failed to achieve B-lymphocyte depletion in the peripheral blood. The period of B-lymphocyte depletion ranged from 3 to 8 months except for one patient who remains depleted at more than 4 yr. Analysis of the regular BILAG assessments showed that improvements occurred in each of the eight organs or systems. The mean daily prednisolone dose fell from 13.8 mg (s.d. 11.3) to 10 mg (s.d. 3.1).
CONCLUSION: In this open study of patients who had failed conventional immunosuppressive therapy, considerable utility in the use of B-cell depletion has been demonstrated. Our data provide strong support for the performance of a full double-blind control trial.

Clinical and immunological effects of Rituximab in patients with lupus nephritis refractory to conventional therapy: a pilot study.
Vigna-Perez M, Hernández-Castro B, Paredes-Saharopulos O, Portales-Pérez D, Baranda L, Abud-Mendoza C, González-Amaro R. Arthritis Res Ther. 2006;8(3):R83.

We studied the clinical and immunological effects of Rituximab (anti-CD20) therapy in patients with lupus nephritis. In an open clinical trial, 22 patients with active systemic lupus erythematosis and renal involvement (mainly class III and IV according to the WHO classification) that was refractory to conventional therapy were

studied. In all these patients, Rituximab (0.5 to 1.0 g at days 1 and 15) was added to the immunosuppressive therapy and its therapeutic effect was evaluated. In addition, the levels and function of regulatory T lymphocytes and the apoptosis of immune cells were assessed. We found a significant reduction in disease activity ($p < 0.05$, MEX-SLEDAI index), and proteinuria ($p < 0.05$) at days 60 and 90 of Rituximab therapy. Although most patients showed improvement in creatinine clearance and erythrocyturia, no significant changes in these parameters were detected. In most patients (20/22), B cell depletion was observed, but no clear-cut effect of Rituximab on complement levels or auto-antibody titers was detected ($p > 0.05$ in all cases). One patient died at day 70 with invasive histoplasmosis. No important adverse effects of Rituximab therapy were registered in other patients. A significant enhancement in the levels of different CD4+ regulatory cells (TREG, Th3, Tr1), but not CD8+ Ts lymphocytes, was observed at day 30. This increase was sustained for TREG cells at day 90, and accompanied by an improvement in their regulatory function. In addition, we observed an unexpected increase in the apoptosis of T cells at day 30. Interestingly, the enhancement in the suppressive function of TREG cells was not observed in the two patients that showed the poorest clinical response to Rituximab. We conclude that the data obtained in this open clinical trial suggest that Rituximab is a promising candidate for randomized controlled trials in patients with lupus nephritis refractory to the conventional immunosuppressive therapy. The effects of Rituximab on regulatory cells and apoptosis of T lymphocytes are interesting and its possible role in the putative effect of this biological agent in systemic lupus erythematosis deserves additional studies.

Rituximab in severe lupus nephritis: early B-cell depletion affects long-term renal outcome.
Melander C, Sallée M, Trolliet P, Candon S, Belenfant X, Daugas E, Rémy P, Zarrouk V, Pillebout E, Jacquot C, Boffa JJ, Karras A, Masse V, Lesavre P, Elie C, Brocheriou I, Knebelmann B, Noël LH, Fakhouri F. Clin J Am Soc Nephrol. 2009 Mar;4(3):579-87.

BACKGROUND AND OBJECTIVES: Standard treatment for lupus nephritis, including corticosteroids and cyclophosphamide, is efficient but is still associated with refractory or relapsing disease, or severe deleterious effects. Rituximab, a monoclonal chimeric anti-B cell antibody, is increasingly used in patients with lupus nephritis, but reported series were small and had a short follow-up. DESIGN, SETTING, PARTICIPANTS, & MEASUREMENTS: The authors analyzed clinical and histologic data of 20 patients who were treated with rituximab for lupus nephritis and followed up for at least 12 mo. RESULTS: Nineteen women and one man received rituximab as induction treatment for an active class IV (15 cases) or class V (5 cases) lupus nephritis. Rituximab was given for lupus nephritis refractory to standard treatment (12 cases), for relapsing disease (6 cases), or as first-line treatment (2 cases). Three patients received cyclophosphamide concomitantly with rituximab. Ten received new injections of rituximab as maintenance therapy. Side effects included mainly five infections and four moderate neutropenias. After a median follow-up of 22 mo, complete or partial renal remission was obtained in 12 patients (60%). Lupus nephritis relapsed in one patient, who responded to a new course of rituximab. The achievement of B cell depletion 1 mo after rituximab, which negatively correlated with black ethnicity and hypoalbuminemia, was strongly associated with renal response. Rapidly progressive glomerulonephritis did not respond to rituximab. CONCLUSION: Rituximab is an interesting therapeutic option in relapsing or refractory lupus nephritis when early B cell depletion is obtained.

Rituximab is an effective treatment for lupus nephritis and allows a reduction in maintenance steroids.
Pepper R, Griffith M, Kirwan C, Levy J, Taube D, Pusey C, Lightstone L, Cairns T. Nephrol Dial Transplant. 2009 Dec;24(12):3717-23.

BACKGROUND: Lupus nephritis is a life-threatening complication of SLE. Treatment regimes include steroids and cyclophosphamide, both associated with significant morbidity. Newer regimes include mycophenolate mofetil (MMF). We report our outcomes in a prospectively monitored cohort of patients receiving our new standard treatment protocol, comprising rituximab induction therapy and MMF maintenance in patients already taking maintenance immunosuppression for SLE who developed lupus nephritis. We then attempted steroid reduction/withdrawal. METHODS: Patients with class III/IV/V lupus nephritis were included. All patients were on steroids prior to the development of lupus nephritis. Eighteen patients have reached at least 1 year follow-up. These patients received rituximab induction therapy and MMF maintenance therapy. Steroid reduction/withdrawal was guided by clinical response. RESULTS: Fourteen of 18 (78%) patients achieved complete or partial remission with a sustained response of 12/18 (67%) at 1 year, with 2 patients having a relapse of proteinuria. Four patients did not respond. There was a significant decrease in proteinuria from a mean protein:creatinine ratio (PCR) of 325 mg/mmol at presentation to 132 mg/mmol at 1 year ($P = 0.004$). Serum albumin significantly increased from a mean of 29 g/L at presentation to 34 g/L at 1 year ($P = 0.001$). The complication rate was low with no severe infections. Following treatment with rituximab, 6 patients stopped prednisolone, 6 patients reduced their maintenance dose and 6 patients remained on the same dose (maximum 10 mg). CONCLUSION: This data demonstrates the efficacy of a rituximab and MMF based regime in the treatment of lupus nephritis, allowing a reduction or total withdrawal of corticosteroids.

B cell depletion as a novel treatment for systemic lupus erythematosus: a phase I/II dose-escalation trial of rituximab.
Looney RJ, Anolik JH, Campbell D, Felgar RE, Young F, Arend LJ, Sloand JA, Rosenblatt J, Sanz I. Arthritis Rheum. 2004 Aug;50(8):2580-9.

OBJECTIVE: Safer and more effective therapies are needed for the treatment of systemic lupus erythematosus (SLE). B lymphocytes have been shown to play fundamental pathogenic roles in SLE, and therefore, elimination of B cells with the use of rituximab may represent a new therapy for SLE. METHODS: A phase I/II dose-escalation trial of rituximab added to ongoing therapy in SLE was conducted. Rituximab was administered as a single infusion of 100 mg/m2 (low dose), a single infusion of 375 mg/m2 (intermediate dose), or as 4 infusions (1 week apart) of 375 mg/m2 (high dose). CD19+ lymphocytes were measured to determine the effectiveness of B cell depletion. The Systemic Lupus Activity Measure (SLAM) score was used as the primary outcome for clinical efficacy. RESULTS: Rituximab was well tolerated in this patient population, with most experiencing no significant adverse effects. Only 3 serious adverse events, which were thought to be unrelated to rituximab administration, were noted. A majority of patients (11 of 17) had profound B cell depletion (to <5 CD19+ B cells/microl). In these patients, the SLAM score was significantly improved at 2 and 3 months compared with baseline (P = 0.0016 and P = 0.0022, respectively, by paired t-test). This improvement persisted for 12 months, despite the absence of a significant change in anti-double-stranded DNA antibody and complement levels. Six patients developed human antichimeric antibodies (HACAs) at a level > or =100 ng/ml. These HACA titers were associated with African American ancestry, higher baseline SLAM scores, reduced B cell depletion, and lower levels of rituximab at 2 months after initial infusion. CONCLUSION: Rituximab therapy appears to be safe for the treatment of SLE and holds significant therapeutic promise, at least for the majority of patients experiencing profound B cell depletion. Based on these results, controlled trials of rituximab appear to be warranted.

Rituximab and mycophenolate mofetil for relapsing proliferative lupus nephritis: a long-term prospective study.
Boletis JN, Marinaki S, Skalioti C, Lionaki SS, Iniotaki A, Sfikakis PP. Nephrol Dial Transplant. 2009 Jul;24(7):2157-60.

BACKGROUND: Subsequent to cyclophosphamide-based induction therapy of lupus nephritis, and despite maintenance chronic immunosuppressive treatment, many patients experience relapses. METHODS: This prospective, observational study included 10 women with biopsy-proven relapse of proliferative lupus nephritis occurring during maintenance with mycophenolate mofetil (MMF) or azathioprine. The long-term outcome after a single course of the B-cell depleting anti-CD20 antibody rituximab (4 weekly infusions of 375 mg/m(2)), combined with daily MMF (2 g) and prednisolone (0.5 mg/ kg/day for 4 weeks, tapered thereafter) is presented. RESULTS: While renal function was not severely impaired at baseline, partial remission (>50% improvement in all abnormal renal parameters) was achieved in eight patients at a median of 3.5 months. In seven patients, with 24-h urinary protein of 2.5 +/- 1.1 g (mean +/- SD), complete remission, associated with increases in serum complement levels and decreases in anti-dsDNA titres, was subsequently established (normal serum creatinine/albumin levels, inactive urine sediment and 24-h urinary protein <0.5 g). Complete nephritis remission was sustained at the follow-up end (median of 38 months) in six patients. Combination treatment was well tolerated. CONCLUSIONS: The efficacy of this low-toxicity combination was particularly evident in patients with subnephrotic proteinuria due to proliferative lupus nephritis relapse. Controlled trials to define the role of rituximab/MMF in this condition are warranted.

Remission of proliferative lupus nephritis following B cell depletion therapy is preceded by down-regulation of the T cell costimulatory molecule CD40 ligand: an open-label trial.
Sfikakis PP, Boletis JN, Lionaki S, Vigklis V, Fragiadaki KG, Iniotaki A, Moutsopoulos HM. Arthritis Rheum. 2005 Feb;52(2):501-13.

OBJECTIVE: Autoreactive B cells play a key role in tissue injury in systemic autoimmune disease, and therefore a treatment resulting in B cell depletion could have benefit. This open-label study was undertaken to evaluate the efficacy of the anti-CD20 monoclonal antibody rituximab in the treatment of lupus nephritis. METHODS: Lupus patients with active proliferative nephritis (4 with focal disease and 6 with diffuse disease) received rituximab (4 weekly infusions of 375 mg/m(2)) combined with oral prednisolone. Clinical, laboratory, and immunologic responses, including peripheral lymphocyte subsets measured by flow cytometry, were prospectively assessed at monthly intervals for 12 months. Complete remission of nephritis was defined as normal serum creatinine and albumin levels, inactive urine sediment, and 24-hour urinary protein <500 mg. Partial remission was defined as >50% improvement in all renal parameters that were abnormal at baseline. RESULTS: B cell depletion lasted from 1 month to 7 months and was well tolerated. Partial remission was achieved in 8 of 10 patients within a median of 2 months (range 1-4 months); in 5 of them, complete remission was subsequently established (at a median of 3 months from baseline), and it was sustained at 12 months in 4. As early as 1 month from baseline, the expression of the costimulatory molecule CD40 ligand on CD4+ T cells was decreased by 4-fold, and it was almost blocked when partial remission was clinically evident. The expression of T cell activation markers CD69

and HLA-DR was significantly decreased at time points when partial remission was observed, and was further decreased during complete remission. In contrast, in patients who did not exhibit a response or when relapse was detected in patients in whom an initial remission had been achieved, such decreases were not prominent. Serum concentrations of double-stranded DNA autoantibodies were decreased in all patients, regardless of clinical outcome. CONCLUSION: Following B cell depletion, clinical remission of lupus nephritis is associated with a decrease in T helper cell activation, suggesting an additional role for B cells, independent of autoantibody production, in promoting disease. A controlled trial to confirm these promising clinical results is warranted.

B lymphocyte depletion therapy in children with refractory systemic lupus erythematosus.
Marks SD, Patey S, Brogan PA, Hasson N, Pilkington C, Woo P, Tullus K. Arthritis Rheum. 2005 Oct;52(10):3168-74.

OBJECTIVE: To determine the safety and efficacy of B lymphocyte depletion therapy in patients with refractory childhood-onset systemic lupus erythematosus (SLE). METHODS: Seven patients (4 of whom were female), ages 7.7-16.1 years (median 14.8 years) with active SLE that was resistant to standard immunosuppressive agents were treated with B cell depletion. During a 2-week period, patients received two 750-mg/m2 intravenous infusions of rituximab, with intravenous cyclophosphamide (if they had not previously received this treatment) and high-dose oral corticosteroids. RESULTS: Patients were followed up for a median of 1.0 years, and no serious adverse effects were noted. In all patients, the clinical symptoms and signs for which rituximab therapy was initiated were improved. There was significant improvement in the British Isles Lupus Assessment Group global scores, from a median score of 22 (range 14-37) at baseline to a median score of 6 (range 4-11) at followup (P = 0.002). In 2 patients with severe multisystem and life-threatening disease unresponsive to standard therapy (including plasma exchange), renal replacement therapy was successfully withdrawn following B cell depletion therapy. These 2 patients have subsequently shown further significant improvement in renal function and proteinuria. CONCLUSION: This open-label study demonstrates that targeted B cell depletion therapy can be a safe and efficacious addition to therapy with standard immunosuppressive agents in patients with refractory childhood SLE. The drugs used for treatment of childhood SLE need to be the most effective, least toxic agents, allowing normal growth and development.

Rituximab therapy for childhood-onset systemic lupus erythematosus.
Willems M, Haddad E, Niaudet P, Koné-Paut I, Bensman A, Cochat P, Deschênes G, Fakhouri F, Leblanc T, Llanas B, Loirat C, Pillet P, Ranchin B, Salomon R, Ulinski T, Bader-Meunier B; French Pediatric-Onset SLE Study Group. J Pediatr. 2006 May;148(5):623-627.

OBJECTIVE: To describe the safety and efficacy of rituximab in the treatment of childhood-onset systemic lupus erythematosus (SLE). STUDY DESIGN: We conducted a French multicenter retrospective study of childhood-onset SLE treated with rituximab. RESULTS: Eleven girls with severe SLE, including 8 girls with class IV or V lupus nephritis, 2 girls with severe autoimmune cytopenia, and 1 girl with antiprothrombin antibody with severe hemorrhage, were treated with rituximab. The mean age at onset of rituximab treatment was 13.9 years. Patients received 2 to 12 intravenous infusions of rituximab (350-450 mg/m2/infusion), with corticosteroids. Six patients also received different standard immunosuppressive agents, including Cyclophosphamide (2 patients). Remission was achieved in 6 of 8 patients with lupus nephritis and in the 2 patients with autoimmune cytopenia. Steroid therapy was tapered in 5 patients who responded to treatment, and low-dose prednisone treatment was maintained in 1 patient. The mean follow-up period was 13.2 months (range, 6-26 months), and remission lasted in all who patients who responded to treatment, except 1 patient who was successfully retreated with a second course of rituximab. Anti-double-stranded DNA antibody levels decreased in 6 of 11 patients, and anticardiolipin antibody levels decreased in 3 of 4 patients. Severe adverse events developed in 5 patients. Effective depletion of peripheral blood B cells was observed in 7 of 8 patients who were examined, and this paralleled the remission. CONCLUSION: Rituximab may be an effective co-therapy; however, further investigations are required because severe adverse events occurred in 45% of the patients in this study.

An open study of B lymphocyte depletion in systemic lupus erythematosus.
Leandro MJ, Edwards JC, Cambridge G, Ehrenstein MR, Isenberg DA. Arthritis Rheum. 2002 Oct;46(10):2673-7.

OBJECTIVE: To gain preliminary evidence for the safety and efficacy of B lymphocyte depletion therapy in refractory systemic lupus erythematosus (SLE). METHODS: Six female patients with active SLE, resistant to standard immunosuppressive therapy, were treated on an open-label basis. During a 2-week period, each patient received two 500-mg infusions of rituximab, two 750-mg infusions of cyclophosphamide, and high-dose oral corticosteroids. RESULTS: No significant adverse events were observed during followup. Patient 1 had not improved at 3 months but was then lost to followup. At 6 months, all 5 remaining patients had improved, as evidenced by improvement in British Isles Lupus Assessment Group global scores, from a median of 14 (range 9-27) at baseline to a median of 6 (range 3-8) at 6 months. Manifestations of SLE such as fatigue, arthralgia/arthritis, and serositis responded particularly well to this protocol. Hemoglobulin levels increased in

patients 2, 3, 5, and 6. The erythrocyte sedimentation rate decreased in patients 2, 3, 4, and 5 and was stable in patient 1. In patients 4 and 5, the urinary protein-to-creatinine ratio decreased significantly. C3 serum levels increased in all 5 patients who had low levels at baseline; in two of these patients, patients 2 and 5, C3 values were normal at 6 months. The variation in the level of anti-double-stranded DNA antibody was different in individual patients. CONCLUSION: This study provides sufficient evidence for the safety and possible efficacy of B lymphocyte depletion therapy in SLE to justify a formal controlled trial.

Tolerance and short term efficacy of rituximab in 43 patients with systemic autoimmune diseases.
Gottenberg JE, Guillevin L, Lambotte O, Combe B, Allanore Y, Cantagrel A, Larroche C, Soubrier M, Bouillet L, Dougados M, Fain O, Farge D, Kyndt X, Lortholary O, Masson C, Moura B, Remy P, Thomas T, Wendling D, Anaya JM, Sibilia J, Mariette X; Club Rheumatismes et Inflammation (CRI). Ann Rheum Dis. 2005 Jun;64(6):913-20.
OBJECTIVE: To assess the tolerance and efficacy of rituximab in patients with various autoimmune diseases seen in daily rheumatological practice. METHODS: 866 rheumatology and internal medicine practitioners were contacted by e-mail to obtain the files of patients treated with rituximab for systemic autoimmune diseases. Patients with lymphoma were analysed if the evolution of the autoimmune disease could be evaluated. RESULTS: In all, 43 of 49 cases could be analysed, including 14 with rheumatoid arthritis (RA), 13 with systemic lupus erythematosus (SLE), six with primary Sjogren's syndrome (pSS), five with systemic vasculitis, and five with other autoimmune diseases. Rituximab was prescribed for lymphoma in two patients with RA and two with pSS. In the 39 other cases, rituximab was given because of the refractory character of the autoimmune disease. The mean follow up period was 8.3 months (range 2 to 26). There were 11 adverse events in 10 patients and treatment had to be discontinued in six. Efficacy was observed in 30 patients (70%): RA 11, SLE 9, pSS 5, vasculitis 2, antisynthetase syndromes 2, sarcoidosis 1. The mean decrease in corticosteroid intake was 9.5 mg/d (range 0 to 50) in responders. Seven patients experienced relapse after mean 8.1 months (5 to 15). Three patients died because of refractory autoimmune disease. CONCLUSIONS: Despite absence of marketing authorisation, rituximab is used to treat various refractory autoimmune diseases in daily rheumatological practice. This study showed good tolerance and short term clinical efficacy, with marked corticosteroid reduction in patients with SLE, pSS, vasculitis, and polymyositis.

Rituximab Therapy in Lupus Nephritis: Current Clinical Evidence.
Ramos-Casals M, Diaz-Lagares C, Soto-Cardenas MJ, Brito-Zeron P, Cuadrado MJ, Sanna G, Bertolaccini L, Khamashta MA. Clin Rev Allergy Immunol. 2010 Apr 24.

The complexity of the therapeutic approach in lupus nephritis (LN) is increased by the large number of patients who do not respond to first-line therapies and by relapses after initial clinical remission. The emergence of biological agents has increased the therapeutic armamentarium available in these complex situations, but their use is limited by the lack of licensing. We analysed current evidence on the therapeutic use of rituximab in adult LN patients by systematic analysis of seven observational studies published since 2005 (four in 2009), which included 106 LN patients treated with rituximab. A complete or partial therapeutic response was achieved in 73 (69%) patients. The response according to the type of LN was stated in 79 cases: 8 (80%) patients with type III LN had a favourable, 26 (67%) of those with type IV, 4 (57%) of those with type V and 18 (78%) of those with mixed membranous-proliferative LN. The main factors associated with no response were younger age, black race and lack of CD19(+) cell depletion. The lowest rates of complete response were observed in patients with type V LN, especially those with associated proliferative lesions. Although it is not yet possible to make definite recommendations, the global analysis of these cases supports the off-label use of rituximab in severe, refractory LN cases.

Anti-CD20 therapy in patients with refractory systemic lupus erythematosus: a longitudinal analysis of 52 Hispanic patients.
Garcia-Carrasco M, Mendoza-Pinto C, Sandoval-Cruz M, Soto-Vega E, Beltran-Castillo A, Jimenez-Hernandez M, Graillet D, Gonzalez L, Rojas-Rodriguez J, Pineda-Almazana A, Zamudio-Huerta L, Lopez-Colombo A. Lupus. 2010 Feb;19(2):213-9.

The objective of this study was to investigate the efficacy and safety of anti-CD20 treatment in Hispanic patients with refractory systemic lupus erythematosus and to determine whether baseline parameters predict disease flare. Fifty-two patients with systemic lupus erythematosus, 13 with active lupus nephritis, eight with thrombocytopenia, three with leukocytopenia, 25 with severe musculoskeletal involvement and three with skin involvement) refractory to conventional therapy were treated with anti-CD20 treatment (rituximab; MabThera, Roche) plus ongoing immunosuppressive treatment. Disease activity was assessed monthly using the SLEDAI validated for the Mexican population with a follow-up period of 6 months. At 6 months of follow-up, significant clinical improvements were detected, with a reduction in the global SLEDAI validated for the Mexican population score. Five of the 13 patients with lupus nephritis (38.4%) had a complete renal response and five (38.4%) had a

partial response. Rituximab was also effective in patients with autoimmune thrombocytopenia, inducing a significant increase in platelet counts (p = 0.012). Nineteen of 25 patients with severe musculoskeletal involvement had remission of arthritis. Only one of the three patients with skin involvement had no lesions at 6 months. Rituximab treatment also allowed a reduction of the oral prednisone dose in the majority of patients. No baseline predictors of flare were found. Treatment was discontinued after the first infusion in two patients due to serum sickness and in another due to pulmonary infection. In conclusion, the addition of rituximab to conventional immunosuppressive therapy may be an effective strategy for lupus nephritis, autoimmune thrombocytopenia and inflammatory polyarthritis in patients with refractory systemic lupus erythematosus.

Effects of rituximab on resistant SLE disease including lung involvement.
Reynolds JA, Toescu V, Yee CS, Prabu A, Situnayake D, Gordon C. Lupus. 2009 Jan;18(1):67-73.

We present a retrospective review of 11 patients with refractory systemic lupus erythematosus (SLE) treated with rituximab after failing corticosteroids and at least one other immunosuppressive drug. We measured clinical response using the Classic British Isles Lupus Assessment Group (BILAG) index, serum complement and reduction in maintenance prednisolone dose. B cells were measured using flow cytometry, and lung function testing was used to assess severe pulmonary disease (three patients). The median patient age was 42 years (range, 25-64) with median disease duration 6 years (range, 2-12). In all, 10 of 11 patients responded initially, with median global BILAG reduction of 7.5 at 6 months (P = 0.007), with loss of all A and B scores by 7 months. Rituximab treatment was associated with normalisation of complement (C3 P = 0.008, C4 P = 0.018) and reduction in steroid requirement, median reduction 15 mg/day (P = 0.036). In 9 of 10 patients who responded, all other immunosuppressants were stopped. There was no significant difference in anti-dsDNA antibody titres in these responders, but they were negative or had low titres at baseline. B-cell depletion continued for median 4 months (range, 2-9), and disease flare occurred at a median 6.6 months (range, 1.5-23) and was preceded by B-cell recovery in all but two patients. Rituximab was beneficial in refractory SLE including severe neurological and cardiorespiratory disease by inducing disease remission, allowing withdrawal of other agents and reduction in steroid requirement. Rituximab appeared to stabilise and possibly improve progressive lung disease.

Use of rituximab in the treatment of refractory systemic lupus erythematosus: Singapore experience.
Lateef A, Lahiri M, Teng GG, Vasoo S. Lupus. 2010;19(6):765-70.

We performed a retrospective study of 10 patients with refractory systemic lupus erythematosus treated with rituximab to determine the efficacy, safety and impact on hospitalization days. Patients received rituximab according to a standardized protocol, all achieved B-cell depletion with clinical improvement in nine patients. At 12 months, BILAG scores improved significantly from a median of 13.5 (range 3-20) at baseline to 1 (range 0-27) (p < 0.05). There was significant reduction in urinary total protein excretion with stabilization of renal function in patients with nephritis. Two out of three patients with thrombocytopenia had normalization of platelet counts. The median duration of B-cell depletion was 6 months (range 6-18). Two patients required retreatment and responded well. There were no adverse outcomes following rituximab therapy. Patients with lupus nephritis spent a median of 17.1 days per year (range 1.9-49) in hospital on conventional treatment which was reduced to 0 days (range 0-14.8, p = 0.027) post-rituximab treatment. The cost of hospitalization was 5989 Singapore dollars per patient-year while on conventional treatment and 5792 Singapore dollars per patient-year post-rituximab. This study adds to the growing literature of rituximab efficacy with potential cost saving in lupus nephritis.

Rituximab in childhood systemic lupus erythematosus refractory to conventional immunosuppression: case report.
Edelbauer M, Jungraithmayr T, Zimmerhackl LB. Pediatr Nephrol. 2005 Jun;20(6):811-3.

Rituximab, a chimeric monoclonal antibody specific for human CD20, has recently been used for the treatment of autoimmune diseases. A 14-year-old patient with severe systemic lupus erythematosus (SLE) and class IV glomerulonephritis presented with immunologic and clinical resistance to conventional immunosuppressive therapy for 10 months after diagnosis. To induce remission of active SLE, treatment with 6 monthly rituximab at 375 mg/m(2), oral mycophenolate and prednisone was initiated followed by maintenance rituximab every 3 months. The SLEDAI decreased significantly from 31 at diagnosis to 14 after nine applications of rituximab. Extrarenal symptoms of SLE improved significantly. However, after induction therapy with rituximab the patient presented a reversible intrinsic acute renal insufficiency for a period of 3 weeks. The discontinuation of the daily medication (oral prednisone and mycophenolate) by the patient herself may explain the progression of active SLE associated with the reversible acute renal failure. Under intensive immunosuppressive therapy improvement of active disease manifestations and stabilization of plasma creatinine concentrations to normal values was observed. However, proteinuria remained elevated and improved only after a protracted period (median protein-to-creatinine ratio 5.2 g/g, range 0.8-11.2 g/g). Hematuria and urinary cell casts persisted. In conclusion, the extrarenal symptoms of the patient responded particularly well to rituximab. However, despite complete B-cell

elimination, renal remission of SLE was not achieved. Thus, it may be possible that humoral and cellular immune mechanisms have a fundamental involvement in the pathogenesis of SLE nephritis.

Off-label use of rituximab in systemic lupus erythematosus: a systematic review.
Murray E, Perry M. Clin Rheumatol. 2010 Jul;29(7):707-16.

Considerable interest in the efficacy of rituximab (a monoclonal CD20 antibody) in patients with systemic lupus erythematosus (SLE) has been generated due to its unique mode of action, culminating in a series of randomized and open trials, and case reports. However, this use is off-license and two significant RCTs have reported negative findings, reopening the debate on clinical benefit. This review of the available data suggests that rituximab induces B-cell depletion in 95% of patients, and a significant reduction in disease activity is achieved with a relatively good safety profile in patients with SLE.

Lupus nephritis: where are we now?
Lightstone L. Curr Opin Rheumatol. 2010 May;22(3):252-6.

PURPOSE OF REVIEW: To consider the challenges in the management of lupus nephritis with respect to diagnosis and optimal therapy for induction and maintenance of response. RECENT FINDINGS: Despite several large clinical trials in lupus nephritis, no second line drug is licensed for use in induction of remission in lupus nephritis. An important issue is how remission and flare are defined and the role of repeat renal biopsies. On the background of negative trials with mycophenolate mofetil and rituximab, there are recent data demonstrating superiority of mycophenolate mofetil in certain subgroups. New data suggest a role for tacrolimus in the treatment of lupus nephritis. Additionally, dogma is being challenged by data showing very low and even no oral steroids can be used in mycophenolate mofetil and rituximab-based regimes. SUMMARY: Despite the negative outcome of recent trials there is growing evidence that there are increasing opportunities in patients with lupus nephritis to offer treatments tailored to the individual needs of the patient based not only on the class and severity of their nephritis but also on their ethnicity, their desire to have children and their predictors of outcome.

B cell-targeted therapies for systemic lupus erythematosus: an update on clinical trial data.
Looney RJ. Drugs. 2010 Mar 26;70(5):529-40.

In the past year there has been remarkable activity and some important success in the development of B cell-targeted therapies for the treatment of systemic lupus erythematosus (SLE). The most promising studies were BLISS-52 and BLISS-76, large phase III studies that demonstrated measurable efficacy for belimumab, a monoclonal antibody against B cell-activating factor (BAFF). The moderate-sized phase II/III trials EXPLORER and LUNAR that tested rituximab, an anti-CD20 monoclonal antibody, for treatment of non-renal and renal lupus, disappointed many investigators with anecdotal success in refractory patients. These rituximab trials were intended to detect a large clinical effect in patients with very active disease and this was not found. Nevertheless, arguments can be made for additional studies in targeted populations or with a change in design to detect smaller or longer-term effects. Epratuzumab, a monoclonal antibody against the B cell surface antigen CD22, and atacicept, a chimeric molecule formed by a receptor for BAFF and a proliferation-inducing ligand (APRIL) with immunoglobulin (Ig)-G, have both been promising in initial small trials and now larger clinical trials are underway. Thus, recent clinical trial data show that B cell-targeting therapies are beginning to fulfil their promise as treatments for SLE and there are good reasons to hope for further progress in the near future.

B-cell-depletion therapy in SLE--what are the current prospects for its acceptance?
Favas C, Isenberg DA. Nat Rev Rheumatol. 2009 Dec;5(12):711-6.

Analogous to the successful introduction of biologic agents to treat rheumatoid arthritis, it was widely envisaged that similar successful studies would follow in systemic lupus erythematosus (SLE), as much was known about the etiopathogenesis of the disease and appropriate agents to block the key cells and molecules were available. The reality, however, has been different. The failure of rituximab, a monoclonal antibody that induces B-cell depletion, to meet its primary and secondary end points in trials of nonrenal SLE (EXPLORER) and renal (LUNAR) lupus nephritis has been disappointing given the success reported in many open-label studies. Concluding that B-cell-depletion therapy is not effective in SLE seems rather extreme. Further analysis of the as-yet unpublished results and their comparison with data from published studies might provide insight into whether B-cell depletion will eventually be accepted as a useful approach for the treatment of SLE.

Rituximab and lupus: good in real life, bad in controlled trials. Comment on the article by Lu et al.
Ramos-Casals M, Díaz-Lagares C, Khamashta MA. Arthritis Rheum. 2009 Sep 15;61(9):1281-2.

A perspective on B-cell-targeting therapy for SLE.
Looney RJ, Anolik J, Sanz I. Mod Rheumatol. 2010 Feb;20(1):1-10.

In recent years, large controlled trials have tested several new agents for systemic lupus erythematosus (SLE). Unfortunately, none of these trials has met its primary outcome. This does not mean progress has not been made. In fact, a great deal has been learned about doing clinical trials in lupus and about the biological and clinical effects of the drugs being tested. Many of these drugs were designed to target B cells directly, e.g., rituximab, belimumab, epratuzumab, and transmembrane activator and calcium modulator and cyclophilin ligand interactor-immunoglobulin (TACI-Ig). The enthusiasm for targeting B cells derives from substantial evidence showing the critical role of B cells in murine models of SLE, as well promising results from multiple open trials with rituximab, a chimeric anti-CD20 monoclonal antibody that specifically depletes B cells (Martin and Chan in Immunity 20(5):517-527, 2004; Sobel et al. in J Exp Med 173:1441-1449, 1991; Silverman and Weisman in Arthritis Rheum 48:1484-1492, 2003; Silverman in Arthritis Rheum 52(4):1342, 2005; Shlomchik et al. in Nat Rev Immunol 1:147-153, 2001; Looney et al. in Arthritis Rheum 50:2580-2589, 2004; Lu et al. in Arthritis Rheum 61(4):482-487, 2009; Saito et al. in Lupus 12(10):798-800, 2003; van Vollenhoven et al. in Scand J Rheumatol 33(6):423-427, 2004; Sfikakis et al. Arthritis Rheum 52(2):501-513, 2005). Why have the controlled trials of B-cell-targeting therapies failed to demonstrate efficacy? Were there flaws in design or execution of these trials? Or, were promising animal studies and open trials misleading, as so often happens? This perspective discusses the current state of B-cell-targeting therapies for human lupus and the future development of these therapies.

Use of rituximab in patients with systemic lupus erythematosus: an update. García-Carrasco M, Jiménez-Hernández M, Escárcega RO, Mendoza-Pinto C, Galarza-Maldonado C, Sandoval-Cruz M, Zamudio-Huerta L, López-Colombo A, Cervera R. Autoimmun Rev. 2009 Feb;8(4):343-8.

Systemic lupus erythematosus (SLE) is a chronic, occasionally life threatening, multisystem disorder. Patients suffer from a wide group of symptoms and have a variable prognosis that depends of the severity and type of organ involvement. The clinical manifestations include fever, skin lesions, arthritis, neurologic, renal, cardiac, and pulmonary disease. The pathogenesis of this serious multisystem autoimmune disease is based on polyclonal B cell immunity, which involves connective tissue and blood vessels. The novel biologic therapies have raised hope for more effective and safer treatment for SLE. Although definitive studies are still under development, the impressive preliminary results of therapies specifically targeting B cells and the signaling pathways involved in B-T-cell interactions suggest that the depletion of memory cells accounts, at least in part, for the clinical efficacy of rituximab therapy in patients whose disease is resistant to other immunosuppressive therapies. However these findings, although provocative, require further investigation in larger cohorts.