SITUATIONS HORS-AMM POUR LESQUELLES L'INSUFFISANCE DES DONNÉES NE PERMET PAS D'ÉVALUER LE RAPPORT BÉNÉFICE/RISQUE

RITUXIMAB

- Myopathies inflammatoires réfractaires à auto-anticorps spécifiques anti-SRP et anti-JO1 (avril 2008)
- Myosites à inclusion (avril 2008)
- Myasthénies réfractaires (avril 2008)
- Syndrome de Gougerot-Sjögren sévère avec manifestations systémiques (avril 2008)
- Hémophilie avec inhibiteurs en échec de tolérance immune (avril 2008)

- En cas de greffe d'organe :
  - Traitement préventif et curatif du rejet de greffe cardiaque (avril 2008)
  - Traitement préventif et curatif du rejet de greffe rénale (avril 2008)
  - Traitement du rejet de greffe hépatique (avril 2008)

- Purpura thrombotique thrombocytopénique grave (défini par une souffrance cérébrale et/ou cardiaque) en association aux échanges plasmatiques (juillet 2011)

- Purpura thrombotique thrombocytopénique en phase de rémission après échanges plasmatiques avec persistance d'un déficit sévère acquis en ADAMTS-13 (activité < 15 % et anticorps détectables par la méthode ELISA (juillet 2011)

- Lupus érythémateux disséminé sévère réfractaire aux immunosuppresseurs et/ou aux échanges plasmatiques (décembre 2011)

Décembre 2011

- **Myopathies inflammatoires réfractaires à auto-anticorps spécifiques anti-SRP et anti-JO1**

Les myopathies inflammatoires à auto-anticorps spécifiques sont des maladies rares ayant une prévalence de 4 cas pour 100 000. Les auto-anticorps anti-JO1 sont présents dans environ 20% des myosites, les auto-anticorps anti-SRP dans 5%. La corticothérapie est le traitement de première intention des myopathies inflammatoires. Elle est efficace au long cours dans plus de 60 à 70% des cas. En cas de résistance primitive ou secondaire, d'intolérance ou de cortico-dépendance, différents immunosuppresseurs ont été proposés.

Les données bibliographiques reposent sur de petites séries cas avec au total 14 sujets traités pour myosites réfractaires. Tous les patients ont répondu au traitement avec amélioration de la force motrice.

Une étude à promotion institutionnelle évaluant le rituximab dans les myopathies inflammatoires à auto-anticorps anti-JO1 et anti-SRP, doit débuter à la Pitié-Salpêtrière.

L'utilisation du rituximab dans les myopathies inflammatoires à auto-anticorps spécifiques anti-SRP et anti-JO1 résistantes au traitement immunosuppresseur et/ou en rechute est insuffisamment documentée à ce jour pour être acceptable en dehors du cadre d'un essai clinique.

Effet du rituximab dans les myosites à Ac spécifiques réfractaires

Auteur principal	Type d'étude	Posologie	Suivi	Critères d'évaluation	Résultats
Levine (2005)	**Ouverte, n=7** Dermatomyosites à Ac antiJO1 réfractaires	RTX[1] : 1 inj/sem pdt 4 semaines	1 an	- Mesure de la force musculaire par dynamométrie - symptômes cliniques : rash, alopécie, capacité vitale forcée	- Amélioration de la force motrice pour 6 patients évaluables de 36 à 113% - Amélioration des signes cliniques Maintien de la réponse à >52 semaines : n=2/7
Arlet (2006)	**Série de cas n=2** Ac anti-SRP	RTX + prednisone + échanges plasmatiques		Force musculaire	Rémission partielle : n=1 Rémission compète : n=1
Gottenberg (2005)	**Série de cas n=2** Polymyosites réfractaires Ac anti-JO1	RTX 375mg/m²/sem pdt 4 sem + prednisone	7 et 5 mois	Force musculaire	Rémission partielle : n=1 Rémission complète : n=1 Rechute à 4 mois pour n=1 Ac anti-JO1 + après tt
Lambotte (2005)	**Cas clinique n=1** Polymyosite réfractaire Ac anti-JO1	RTX		Force musculaire	Amélioration clinique
Chiappetta (2005)	**Cas clinique n=1**	RTX 100 mg/m²/sem x6 + autres immuno-suppresseurs		Force musculaire CPK	Amélioration clinique

[1]RTX: rituximab

Bibliographie

1. Arlet JB, Dimitri D, Pagnoux C, Boyer O, Maisonobe T, Authier FJ, Bloch-Queyrat C, Goulvestre C, Heshmati F, Atassi M, Guillevin L, Herson S, Benveniste O, Mouthon L. Marked efficacy of a therapeutic strategy associating prednisone and plasma exchange followed by rituximab in two patients with refractory myopathy associated with antibodies to the signal recognition particle (SRP).Neuromuscul Disord. 2006 May; 16(5):334-6.

2. Chiappetta N, Steier J, Gruber B. Rituximab in the treatment of refractory dermatomyositis. J Clin Rheumatol. 2005 Oct; 11(5):264-6

3. Lambotte O, Kotb R, Maigne G, Blanc FX, Goujard C, Delfraissy JF. Efficacy of rituximab in refractory polymyositis. J Rheumatol. 2005 Jul;32(7):1369-70.

4. Levine TD. Rituximab in the treatment of dermatomyositis: an open-label pilot study. Arthritis Rheum. 2005 Feb; 52(2):601-7.

5. 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. Tolerance and short term efficacy of rituximab in 43 patients with systemic autoimmune diseases. Ann Rheum Dis. 2005 Jun; 64(6):913-20.

Résumé-abstract

Levine TDRituximab in the treatment of dermatomyositis: an open-label pilot study. . Arthritis Rheum. 2005 Feb;52(2):601-7.

OBJECTIVE: To test the hypothesis that B cells play a role in the pathophysiology of dermatomyositis (DM) by examining the effect of B cell depletion in patients with symptomatic DM. Patients were treated with rituximab, a CD20+ B cell-depleting monoclonal antibody. METHODS: This was an open-label uncontrolled pilot trial in 7 adult patients with DM, 6 of whom had longstanding illness that was responding inadequately to a number of currently available immunosuppressive agents. All patients received 4 intravenous infusions of rituximab given at weekly intervals. Patients were followed up for up to 1 year without further treatment with rituximab. One patient was lost to followup. The principal efficacy outcome was muscle vital capacity, improved markedly in patients with these symptoms. Rituximab was well tolerated, with strength, measured by quantitative dynomometry. RESULTS: All 6 evaluable patients exhibited major clinical improvement, with muscle strength increasing over baseline by 36-113%. Maximal improvements in muscle strength occurred as early as 12 weeks after the initial infusion of rituximab. CD20+ B cells were effectively depleted in all patients by 12 weeks. Four patients experienced a return of symptoms that coincided with the return of B cells before the 52-week end point. Two patients maintained their increased muscle strength at 52 weeks, and 1 of these patients maintained this strength even after the return of B cells. Other symptoms of DM, including rash, alopecia, and reduced forced no treatment-related severe or serious adverse events during the observation period of this study. CONCLUSION: This small open-label study of DM patients treated with rituximab provided sufficiently encouraging results to justify a more formal evaluation of the value of B cell depletion therapy in the treatment of DM.

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.Tolerance and short term efficacy of rituximab in 43 patients with systemic autoimmune diseases. 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.

Arlet JB, Dimitri D, Pagnoux C, Boyer O, Maisonobe T, Authier FJ, Bloch-Queyrat C, Goulvestre C, Heshmati F, Atassi M, Guillevin L, Herson S, Benveniste O, Mouthon L. Marked efficacy of a therapeutic strategy associating prednisone and plasma exchange followed by rituximab in two patients with refractory myopathy associated with antibodies to the signal recognition particle (SRP). Neuromuscul Disord. 2006 May;16(5):334-6.

We report two patients with myopathy associated with anti-signal recognition particle Ab, refractory to conventional therapy, who were treated with prednisone and plasma exchange, followed by rituximab. A marked response was observed in both patients, with partial to complete recovery of muscle strength, which was sustained.

Lambotte O, Kotb R, Maigne G, Blanc FX, Goujard C, Delfraissy JF.Efficacy of rituximab in refractory polymyositis. J Rheumatol. 2005 Jul;32(7):1369-70.

We describe the effectiveness of rituximab, an anti-B lymphocyte monoclonal antibody, in a case of refractory polymyositis with interstitial pulmonary disease and anti-Jo-1 autoantibody (antisynthetase syndrome). Rituximab was well tolerated, and its efficacy in inflammatory myositis should be evaluated.

Chiappetta N, Steier J, Gruber BRituximab in the treatment of refractory dermatomyositis. . J Clin Rheumatol. 2005 Oct; 11(5):264-6

Dermatomyositis is an inflammatory myopathy characterized by muscle weakness and inflammation. In contrast to polymyositis and inclusion body myositis, humoral immune mechanisms appear to contribute to the pathogenesis of dermatomyositis. A 56-year-old man with dermatomyositis resistant to conventional therapies was treated with 6 weekly infusions of the anti-CD-20 monoclonal antibody, rituximab, at a dosage of 100 mg/m in addition to other agents. The patient demonstrated a remarkable clinical response as indicated by an increase in muscle strength and a decline in creatine kinase enzymes. B-cell depletion therapy with rituximab used alone or in combination with other immunosuppressive therapies may be a viable option in patients with dermatomyositis as well as other autoimmune diseases refractory to current therapies.

- **Myosites à inclusion**

Les myosites à inclusions sont les myopathies inflammatoires les plus fréquentes au-delà de 50 ans. Elles évoluent spontanément vers une aggravation lente et progressive. Elles sont résistantes à la corticothérapie et ne répondent que rarement aux immunosuppresseurs.

On ne retrouve pas de données bibliographiques dans la littérature scientifique évaluant l'effet du rituximab dans cette pathologie.

- **Myasthénies réfractaires**

La myasthénie est une maladie de la jonction neuromusculaire de type auto-immun. Les auto-anticorps se fixent aux récepteurs post-synaptiques de l'acétylcholine et altèrent la transmission de l'influx nerveux. La prévalence de la myasthénie est de 43 à 64 cas par million et l'incidence de 2 à 5 cas/an/million. On observe 2 pics de fréquence de la maladie, l'un avant 35 ans avec une nette prédominance féminine et l'autre après 50 ans.

Une myasthénie peut être considérée comme étant réfractaires aux traitements conventionnels en cas d'échec à au moins un traitement de première intention par prednisone, azathioprine, méthotrexate, cyclophosphamide, cyclosporine, IgIV et/ou échanges plasmatiques. L'échec est défini comme une absence d'amélioration et/ou dégradation des paramètres évalués conduisant le clinicien à réintroduire d'autres traitements.

Les données scientifiques du rituximab dans les myasthénies réfractaires sont insuffisantes avec 3 cas publiés. Une étude à promotion institutionnelle évaluant le rituximab dans les myasthénies réfractaires doit débuter à la Pitié-Salpêtrière.

Bibliographie

1. Gajra A, Vajpayee N, Grethlein SJ. Response of myasthenia gravis to rituximab in a patient with non-Hodgkin lymphoma. Am J Hematol. 2004 Oct; 77(2):196-7.

2. Takagi K, Yoshida A, Iwasaki H, Inoue H, Ueda T. Anti-CD20 antibody (Rituximab) therapy in a myasthenia gravis patient with follicular lymphoma. Ann Hematol. 2005 Aug; 84(8):548-50.

3. Wylam ME, Anderson PM, Kuntz NL, Rodriguez V. Successful treatment of refractory myasthenia gravis using rituximab: a pediatric case report. J Pediatr. 2003 Nov; 143(5):674-7.

Résumé-abstract

Gajra A, Vajpayee N, Grethlein SJ. Response of myasthenia gravis to rituximab in a patient with non-Hodgkin lymphoma. Am J Hematol. 2004 Oct;77(2):196-7.

Myasthenia gravis is a B-cell-mediated autoimmune neuromuscular disorder characterized by weakness and fatigability of skeletal muscles. The underlying defect is an autoantibody-mediated attack on the acetylcholine receptors (AchRs) at the neuromuscular junction. Rituximab is a genetically engineered chimeric murine/human monoclonal antibody indicated for treatment of patients with low-grade or follicular, CD20-positive, B-cell non-Hodgkin lymphoma. Based on its potential for elimination of auto-reactive B-cell clones, rituximab may have a role in the management of some autoimmune disorders. We report a patient with B-cell, follicular non-Hodgkin lymphoma and a long-standing history of myasthenia gravis and the favorable impact of rituximab on both disorders.

Wylam ME, Anderson PM, Kuntz NL, Rodriguez V. Successful treatment of refractory myasthenia gravis using rituximab: a pediatric case report. J Pediatr. 2003 Nov;143(5):674-7.

We report the successful use of anti-CD20 therapy in a child with refractory myasthenia gravis (MG), an antibody-mediated autoimmune disease, who did not respond to conventional therapy. After initiation of anti-CD20 therapy, clinical improvement (muscular strength, pulmonary function) was observed.

- **Syndrome de Gougerot-Sjögren sévère avec manifestations systémiques**

Le syndrome de Gougerot-Sjögren est une maladie d'origine auto-immune touchant les glandes exocrines. Si, dans la majorité des cas, l'atteinte est bénigne (« syndrome sec ») et le traitement essentiellement symptomatique, il existe également des formes systémiques rares et graves *(fibrose interstitielle diffuse résistante à la corticothérapie et aux immunosuppresseurs, vascularite cérébrale avec présentation pseudo-psychiatrique…).* La prévalence du syndrome de Gougerot-Sjögren est estimée entre 1 et 3%. C'est une des maladies auto-immunes systémiques les plus fréquentes après la polyarthrite rhumatoïde. Il n'existe aucun traitement de fond validé dans le syndrome de Gougerot-Sjögren.

Une étude rétrospective de faible niveau de preuve (Seror, 2007) a porté sur 16 patients, dont 5 ayant un lymphome (qui est une indication d'AMM pour le rituximab) a montré une amélioration clinique de 9 patients sur 11.

Une étude ouverte menée dans le cadre d'un PHRC à Brest (Devauchelle-Pensec, 2005) a évalué le rituximab en monothérapie chez des patients ayant un syndrome de Gougerot-Sjögren primaire actif. L'activité de la maladie était évaluée au moyen de 4 échelles visuelles analogiques (EVA) (0-100mm), qui mesuraient l'activité globale, l'asthénie, l'intensité douloureuse et le syndrome sec. Les patients inclus devaient présenter un score > 50 mm pour au moins 2 des 4 échelles. A 12 semaines, après 2 doses de rituximab (375 mg/m²), une amélioration subjective du syndrome sec, ce qui est fréquent dans le syndrome de Gougerot-Sjögren où la composante psychologique est importante, a été observée mais sans amélioration clinique objective (test de Schirmer, taux basal du flux salivaire). Pour l'unique patient qui présentait une atteinte pulmonaire à l'inclusion, une rémission rapide et complète a été obtenue après traitement. L'étude n'a pas été publiée.

D'autres séries de cas publiées ont également montré une amélioration clinique subjective du syndrome de Gougerot-Sjögren après traitement par rituximab (Pijpe, 2005 ; Gottenberg, 2005). Cependant la population pouvant être traitée est mal définie, la sévérité de la maladie n'est pas précisée et les éléments d'efficacité sont peu clairs. La seule étude potentiellement intéressante (Voulgarelis 2004) semble montrer une amélioration de la neuropathie, mais repose sur 4 cas

Un PHRC est actuellement en cours : Etude TEAR: tolérance et efficacité du rituximab dans le Syndrome de Sjögren. Etablissement promoteur CHU de Brest, investigateur principal : Pr SARAUX.

Effet du rituximab dans le syndrome de Gougerot-Sjögren

Auteur principal	Type d'étude	Posologie	Suivi	Critères d'évaluation	Résultats
Seror (2007)	**Rétrospective n=16** Patientes ayant des complications systémiques - lymphome (n=5) - atteinte pulmonaire avec polysynovite (n=2) - polysynovite sévère (n=2) - cryoglobulinémie (n=5) - thrombocytopénie (n=1) - mononeuropathie (n=1)	Rituximab: 375mg/m²/sem pdt 4 semaines Pré Rituximab: +prednisone + clemastine	14.5 mois [2-48]	Amélioration clinique et biologique	<u>Effet sur les lymphomes</u>: Rémission clinique complète : n=4/5 <u>Effet sur les signes systémiques</u> : Amélioration clinique : n=9/11 . *cryoglobulinémie* : disparition de l'atteinte cutanée n=5/5 . *polysynovite, atteinte pulmonaire ou rénale* rémission complète de l'atteinte articulaire n=1 amélioration de l'atteinte pulmonaire, ou rénale ou articulaire n= 3 . *mononeuropathie* amélioration n=1 . *atteinte glandullaire* amélioration n=3 <u>Effet biologique</u> ↓ lymphocytes B (n=14/15) avec re-augmentation chez 3 patients à 9, 16 et 18 mois ↓ VS et CRP ↓ facteur rhumatoïde avec disparition chez 5 patients
Pijpe (2005)	**Série de cas n=15** Sjögren primaire associé à un lymphome MALT (n=7)	Rituximab: 375mg/m²/sem pdt 4 semaines Pré Rituximab: + prednisone + clemastine	12 sem	Evaluation à l'inclusion, à S5 et S12 : - fonction salivaire - fonction lacrymale - subjective par le patient (EVA, MFI, SF-36[4]) - gradation lymphome MALT à S12	<u>RC [6] lymphome MALT:</u> n=3/7 ; Aggravation : n=1/7 <u>Fonction salivaire :</u> - sécrétion totale : non modifiée - ↑ sécrétion sous-mandibulaire et sous-linguale <u>Fonction lacrymale :</u> - ↑ score Rose Bengal <u>Evaluation subjective :</u> amélioration significative de la sécheresse buccale diurne et nocturne, et de la dysphagie chez 7 patients ayant un Sjögren sans lymphome de MALT

Auteur principal	Type d'étude	Posologie	Suivi	Critères d'évaluation	Résultats
					Arrêt prématuré pour EI : n=3/15 (tableau fièvre + arthrite + myalgies graves)
Devauchelle-Pensec (2005)	**Série de cas n=16** Sjögren primaire *Abstract*	Rituximab: 375 mg/m²/sem pdt 2 semaines	12 sem	Examen clinique Biologie Qualité de vie Sécheresse oculaire et buccale Echo-doppler glandes salivaires	- Amélioration subjective du syndrome sec et de l'asthénie - Pas d'amélioration objective du syndrome sec (test Schirmer, taux basal du flux salivaire) - Rémission manifestations pulmonaires : n=1/1 - Taux autoAc non modifiés
Gottenberg (2005)	**Série de cas n=6**	Rituximab: 375mg/m²/sem pdt 2 à 4 semaines	6 à 11 mois	- Symptômes extra-glandulaires - EVA sécheresse et asthénie - AutoAc anti-SSA et anti-SSB	- Amélioration symptômes extra-exocrines : n=5/6 - ↓scores EVA sécheresse et asthénie - ↓ corticothérapie n= 5/6 - Persistance des auto-Ac
Voulgarelis (2004)	**Série de cas n=4** Sjögren associé à un LNH agressif à cellules B (+cryoglobulinémie mixte type II n=3)	Rituximab: 375mg/m² à chaque premier jour de cycle CHOP ; 8 cycles CHOP au total.	10 à 23 mois	- RC lymphome - Manifestations systémiques (neuropathie, lymphadénopathies, purpura, anémie, arthralgies) - Titres ANA, autoAc anti-SSA et anti-SSB	- RC lymphome : n=4/4 - Disparition cryoglobulinémie (n=3/3) et purpura (n=3/3) ; amélioration neuropathie (n=2/2). - Titres ANA et autoAc non modifiés

EVA: échelle visuelle analogique mesurant la sécheresse buccale et oculaire ;
MFI: Multidimensional Fatigue Inventory : échelle comprenant 20 items évaluant l'asthénie et validée pour le syndrome de Sjögren (plus le score est élevé, plus l'asthénie est importante) ;
SF-36 : questionnaire mesurant la qualité de vie (un score élevé reflète un bon niveau de qualité de vie) ;
titre ANA : anticorps antinucléaire ;
RC : rémission complète.

Bibliographie

1. Seror R, Sorde C, Guillevin L, Hachulla E, Masson C, Ittah M, Candon S, Le Guern V, Aouba A, Sibilia J, Gottenberg JE, Mariette X. Tolerance and efficacy of rituximab and changes in serum B cell biomarkers in patients with systemic complications of primary Sjögren's syndrome. Ann Rheum Dis, Mar 2007; 66: 351 – 357

2. Devauchelle-Pensec V., Morvan J., Pennec Y., Pers J.O., Jamin C, Jousse-Joulin S., Roudaut A., Cochener B., Quintin-Roué I., Renaudineau Y., Youinou P., Saraux A. Rituximab (anti-CD20) in the treatment of primary Sjögren's syndrome (PSS): Results of an open label study (PHRC Brest 2003).

3. 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). Tolerance and short term efficacy of rituximab in 43 patients with systemic autoimmune diseases. Ann Rheum Dis. 2005 Jun; 64(6):913-20.

4. Harner KC, Jackson LW, Drabick JJ. Normalization of anticardiolipin antibodies following rituximab therapy for marginal zone lymphoma in a patient with Sjogren's syndrome. Rheumatology (Oxford). 2004 Oct; 43(10):1309-10.

5. Pijpe J, van Imhoff GW, Spijkervet FK, Roodenburg JL, Wolbink GJ, Mansour K, Vissink A, Kallenberg CG, Bootsma H. Rituximab treatment in patients with primary Sjogren's syndrome: an open-label phase II study. Arthritis Rheum. 2005 Sep; 52(9):2740-50.

6. Ring T, Kallenbach M, Praetorius J, Nielsen S, Melgaard B. Successful treatment of a patient with primary Sjogren's syndrome with Rituximab. Clin Rheumatol. 2005 Nov 8; 1.

7. Voulgarelis M, Giannouli S, Anagnostou D, Tzioufas AG. Combined therapy with rituximab plus cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP) for Sjogren's syndrome-associated B-cell aggressive non-Hodgkin's lymphomas. Rheumatology (Oxford). 2004 Aug; 43(8):1050-3.

Résumé-abstract

Seror R, Sorde C, Guillevin L, Hachulla E, Masson C, Ittah M, Candon S, Le Guern V, Aouba A, Sibilia J, Gottenberg JE, Mariette X. Tolerance and efficacy of rituximab and changes in serum B cell biomarkers in patients with systemic complications of primary Sjögren's syndrome. Ann Rheum Dis, Mar 2007; 66: 351 – 357

Objective: To investigate the safety and efficacy of rituximab (RTX) for systemic symptoms in patients with primary Sjögren's syndrome (pSS), and changes in B cell biomarkers. Patients and methods: The records of 16 patients with pSS according to the American European consensus group criteria were reviewed retrospectively. Results: Patients, all women, had a median age of 58.5 (range 41–71) years and a disease duration of 9.5 (range 0–25) years. RTX was prescribed for lymphoma (n = 5), refractory pulmonary disease with polysynovitis (n = 2), severe polysynovitis (n = 2), mixed cryoglobulinaemia (n = 5), thrombocytopenia (n = 1) and mononeuritis multiplex (n = 1). The median follow-up duration was 14.5 (range 2–48) months. Three patients experienced adverse events, including one mild serum sickness-like reaction with the presence of human antichimeric antibodies. Efficacy of treatment was observed in 4 of 5 patients with lymphomas and in 9 of 11 patients with systemic involvement. Dryness was improved in only a minority of patients. Corticosteroid dose was reduced in 11 patients. RTX induced decreased rheumatoid factor, ?-globulin and ß2-microglobulin levels, and the level of B cell activating factor of the tumour necrosis factor family (BAFF) increased concomitantly with B cell depletion. Five patients were re-treated, with good efficacy and tolerance, except for one with probable serum sickness-like reaction. Conclusion: This study shows good efficacy and fair tolerance of RTX for systemic features. In addition, RTX allows for a marked reduction in corticosteroid use. Except for BAFF, the level of which increases, serum B cell biomarker levels decrease after taking RTX. Controlled trials should be performed to confirm the efficacy of RTX in pSS.

Pijpe J, van Imhoff GW, Spijkervet FK, Roodenburg JL, Wolbink GJ, Mansour K, Vissink A, Kallenberg CG, Bootsma H. Rituximab treatment in patients with primary Sjogren's syndrome: an open-label phase II study. Arthritis Rheum. 2005 Sep;52(9):2740-50.

OBJECTIVE: To investigate the safety and efficacy of B cell depletion treatment of patients with active primary Sjogren's syndrome of short duration (early primary SS) and patients with primary SS and mucosa-associated lymphoid tissue (MALT)-type lymphoma (MALT/primary SS). METHODS: Fifteen patients with primary SS were included in this phase II trial. Inclusion criteria for the early primary SS group were B cell hyperactivity (IgG >15 gm/liter), presence of autoantibodies (IgM rheumatoid factor, anti-SSA/SSB), and short disease duration (<4 years). Inclusion criteria for the MALT/primary SS group were primary SS and an associated MALT-type lymphoma (Ann Arbor stage IE) localized in the parotid gland. Patients were treated with 4 infusions of rituximab (375 mg/m2) given weekly after pretreatment with prednisone (25 mg) and clemastine. Patients were evaluated, using immunologic, salivary/lacrimal function, and subjective parameters, at baseline and at 5 and 12 weeks after the first infusion. RESULTS: Significant improvement of subjective symptoms and an increase in salivary gland function was observed in patients with residual salivary gland function. Immunologic analysis showed a rapid decrease of peripheral B cells and stable levels of IgG. Human anti-chimeric antibodies (HACAs) developed in 4 of 15 patients (27%), all with early primary SS. Three of these patients developed a serum sickness-like disorder. Of the 7 patients with MALT/primary SS, complete remission was achieved in 3, and disease was stable in 3 and progressive in 1. CONCLUSION: Findings of this phase II study suggest that rituximab is effective in the treatment of primary SS. The high incidence of HACAs and associated side effects observed in this study needs further evaluation.

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). Tolerance and short term efficacy of rituximab in 43 patients with systemic autoimmune diseases. 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.

Ring T, Kallenbach M, Praetorius J, Nielsen S, Melgaard B. Successful treatment of a patient with primary Sjogren's syndrome with Rituximab. Clin Rheumatol. 2005 Nov 8; 1.

We report the course of a 55-year-old woman, the first patient with primary Sjogren's syndrome and distal renal tubular acidosis but without lymphoma to be treated with B-cell depletion using Rituximab. Rapidly after B-cell depletion, remarkable improvement in xerostomia occurred, while serological findings and tubular acidosis have been unchanged. In labial salivary gland biopsy, lymphocyte infiltration and particularly CD20-positive cells decreased strikingly. Aquaporin 1 (AQP-1) expression in myoepithelial cells was very low before treatment and increased noticeably. Apical AQP-5 in acinus cells likewise increased following Rituximab. In contrast, basolateral NKCC1 was expressed at unchanged intensity before and following Rituximab. The improvement has been sustained and still is most gratifying 10 months after treatment. B-cell depletion may be effective treatment in Sjogren's syndrome. Likewise, it may now be possible to separate the immunologic phenomena in Sjogren's syndrome from the consequences of prolonged hyposalivation when studying the pathophysiology of xerostomia.

Voulgarelis M, Giannouli S, Anagnostou D, Tzioufas AG. Combined therapy with rituximab plus cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP) for Sjogren's syndrome-associated B-cell aggressive non-Hodgkin's lymphomas. Rheumatology (Oxford). 2004 Aug;43(8):1050-3.

OBJECTIVE: To determine the safety and therapeutic response of a regimen consisting of cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP) plus rituximab in patients with Sjogren's syndrome (SS) and aggressive non-Hodgkin's lymphoma (NHL). METHODS: Four SS patients with aggressive marginal zone NHL were enrolled in this trial. All patients were classified according to the newly proposed revised European-American classification of lymphoid neoplasms. Three out of four patients also had mixed cryoglobulinaemia (MC) of type II. They were treated every 3 weeks for eight cycles of CHOP. Patients also received rituximab, at a dose of 375 mg per square metre, on day 1 of each of the eight cycles of CHOP. Four weeks after completion of the eighth course of CHOP plus rituximab and every 6 months thereafter, patients were re-evaluated for response. RESULTS: Complete remission of lymphoma was achieved in all four patients. The lymphoma patients remained in remission for a period of 23, 15, 12 and 10 months respectively, while certain signs and symptoms of MC type II (purpura, peripheral neuropathy and arthralgias) significantly improved with treatment. In addition, the titres of circulating cryoglobulins and RF decreased, while C4 levels returned to normal. CONCLUSION: CHOP plus rituximab was well tolerated and proved effective in SS patients with aggressive NHL. Our observations may warrant a larger controlled trial to assess the effectiveness of this regimen in such patients.

V. Devauchelle-Pensec, J. Morvan1, Y. Pennec, J. O. Pers, C. Jamin, S. Jousse-Joulin, A. Roudaut, B. Cochener, I. Quintin-Roué, Y. Renaudineau, P. Youinou3 A. Saraux. Rituximab (anti-CD20) in the treatment of primary Sjögren's syndrome (PSS): Results of an open label study (PHRC Brest 2003)

BACKGROUND: Current pharmacology treatments for primary Sjögren's syndrome (pSS) have been unsuccessful on symptoms and have no impact on its course. B lymphocyte depletion has recently emerged as a promising treatment of autoimmune diseases. OBJECTIVES: To investigate the safety and efficacy of a chimeric anti-CD20 monoclonal antibody (Rituximab) without corticosteroid adjunction in the treatment of patients with active pSS, we conducted an open label study.Methods: 16 patients with pSS received Rituximab infusions (375mg/m2) at weeks 0 and 1 and were followed up for 12 weeks. All patients fulfilled the new American-European consensus group criteria for pSS and had an active disease active disease as assessed by values >50 mm on 2 of 4 visual analog scales (VAS) (0-100 mm) that evaluated global activity of the disease, fatigue, global pain, and dryness. They underwent exhaustive, standardized evaluations included clinical examination, biologic parameters, objective dry mouth and dry eye evaluation, histological parameters, ultrasonographic evaluation (ultrasound and Doppler) of tender points and salivary gland, and quality of life assessments. RESULTS: Infusions were well tolerated, excepted for one patient who presented an infusion-reaction who rapidly resolved with a lower speed of infusion. A second patient experienced 7 days after the second infusion arthralgia and purpura. At week 12, all patients had a complete depletion in CD20. Different subjective parameters including fatigue and dryness were improved ($p<0.05$). There was no difference in objective evaluation of the dryness (Schirmer test, unstimulated salivary flow rate) but Doppler waveform analysis of

salivary glands showed significant differences. One patient had pulmonary manifestations at week 0 which rapidly and completely disappeared after treatment. We did not observe any modification in autoantibodies levels. CONCLUSION: Although from a small, open-label study, these results suggest that Rituximab holds promise for treating pSS and we conclude that: (1) Low doses of Rituximab promoted an acute and complete CD20 depletion in the serum. (2) Low dose Rituximab infusions are well tolerated without corticosteroid in pSS (3) Pulmonary manifestations of pSS could respond successfully to Rituximab (4) Patients had a statistically significant favorable response in subjective criteria such as fatigue and dryness. Larger, controlled studies are needed.

- **Hémophilie avec inhibiteurs en échec de tolérance immune**

Il n'existe pas de données d'efficacité concernant l'utilisation du rituximab dans l'hémophilie avec inhibiteurs en échec de tolérance immune.

- **Traitement préventif et curatif du rejet de greffe cardiaque**

Traitement curatif du rejet de greffe cardiaque

Le rejet humoral en transplantation cardiaque est une pathologie rare, qui touche moins de 50 patients en France chaque année.

La littérature concernant l'utilisation du rituximab repose sur 4 publications de cas rapportés sur l'utilisation du rituximab dans le traitement de rejet aigu et humoral.
- La première observation est un cas historique publié par Aranda en 2002.
- De façon anecdotique, un deuxième cas publié par Baran en 2004; fait état de l'efficacité du rituximab dans le traitement d'un rejet humoral survenant deux ans après transplantation réversible après une dose de rituximab.
- Un cas publié par Garrett en 2002 fait état d'un patient traité pour un rejet vasculaire par rituximab après efficacité de la plasmaphérèse.
- La quatrième publication est de ce même auteur (Garrett, 2005). Elle fait état de 8 patients présentant un rejet à médiation humorale sur 53 patients transplantés sur la même période et traités par 375 mg/m² de surface corporelle par semaine de rituximab pendant 4 semaines, soit une incidence de rejet humoral de 15%. Un patient a été traité deux fois pour récidive de rejet humoral à 15 mois. Le délai entre la transplantation et la survenue de rejet humoral était de 6 mois à 51 mois, pour les 8 patients. La chute moyenne de la fraction d'éjection ventriculaire gauche était d'environ 50% de la valeur de référence avec une récupération quasi *ad integrum* après traitement par rituximab. L'évolution des patients a été satisfaisante avec notamment une très faible incidence de maladie vasculaire du greffon puisqu'un seul patient (celui qui a présenté les 2 épisodes) a présenté une maladie vasculaire du greffon alors que l'on sait que les rejets à médiation humorale représentent un facteur de risque important de survenue de maladie vasculaire du greffon. L'incidence des complications infectieuses au décours du traitement par rituximab a été habituelle de 0,25 infection par patient et par an c'est-à-dire comparable aux données de la littérature.

La faible incidence du rejet humoral ou du rejet mixte à composante humorale rend toute étude randomisée impossible, ce d'autant que les critères de diagnostic du rejet humoral ne sont pas standardisés même si la détection de l'expression de C4d sur les biopsies constitue une avancée considérable dans le diagnostic du rejet humoral. Cependant, la sensibilité de ce test est comprise entre 31 et 81 %.

Le niveau de preuve du rituximab dans le traitement curatif du rejet de greffe cardiaque est faible. Compte tenu du degré d'extrême urgence de la situation, la prescription de rituximab ne peut être formellement exclue en sauvetage d'un rejet humoral en association aux immunoglobulines IV et/ou aux échanges plasmatiques, avec une incertitude sur la durée du traitement et notamment le nombre d'injections, soit 4

injections de façon similaire au « protocole lymphome » alors que dans une étude une seule injection s'est avérée suffisante. Cette situation est exceptionnelle.

Effet du rituximab dans le traitement curatif du rejet de greffe cardiaque

Auteur principal	Type d'étude	Posologie	Suivi	Critères d'évaluation	Résultats
Garrett (2002)	**Cas clinique n=1**	Rituximab : 375 mg/m² (750mg au total) pdt 4 sem	1 an	FEVG Biopsies greffon	- FEVG de 0.30 pré-tt à 0.60 post-tt - Biopsies dans l'année post-tt : pas de rejet humoral, rejet cellulaire grade 0 à 1A Tolérance : Toxoplasmose à 1 an post-tt
Garrett (2005)	**Série de cas n=8**	Rituximab : 375 mg/m²/sem pdt 4 sem	4 à 42 mois (15 mois en moyenne)	Biopsie greffon cardiaque 1 à 2 sem post-tt FEVG Coronarographie pour 6 patients	- FEVG : de 43% lors du rejet à 53% post-tt - Biopsie : négativation du marquage IgG et C' - Coro : pas de modification pour 5 patients ; coronaropathie post-rejet ayant nécessité angioplastie avec stent à 6 mois post-tt et décès à 21 mois post-tt (n=1) - Décès : n=1 Tolérance : - Toxoplasmose pulmonaire : n=1 (11 mois d'hospitalisation) + infection urinaire - Sepsis sur PNA à 2 sem post-tt : n=1 - Sternite à 11 mois post- tt : n=1 - Cancer pulm avec métas osseuses à 20 mois post-tt
Aranda (2002)	**Cas clinique n=1** Rejet mixte humoral et cellulaire	Rituximab: 375 mg/m²/sem pdt 4 sem	1 an	Biopsie greffon à 1 an FEVG Coronarographie	- Biopsie à 1 an : pas de rejet humoral, rejet cellulaire modéré - FEVG normale - coro normale à 9 mois Tolérance : Pas d'infection virale ni bactérienne
Baran (2004)	**Cas clinique n=1**	Rituximab dose unique à 375 mg/m²	2 ans	Biopsie greffon Coronarographie à 1an	- Biopsie J10 post-rituximab: pas de rejet humoral, rejet cellulaire modéré - Coronarographie à 1 an normale - Pas de récidive de rejet Tolérance : ?

Traitement préventif du rejet de greffe cardiaque

Aucune étude randomisée n'a évalué l'effet du rituximab chez le patient hyperimmunisé ou immunisé en vue d'une transplantation cardiaque, bien que ce type d'étude soit possible et envisageable.

Néanmoins, en pratique, le rituximab est actuellement utilisé dans le protocole de désimmunisation anti-HLA en pré-transplantation après échec des immunoglobulines à haute dose. La prise en charge de ces patients doit se faire dans les plus brefs délais pour que le patient ait le maximum de chance d'être désensibilisé afin d'être transplanté dans une fenêtre immunologique favorable pour éviter la mise en place d'une assistance circulatoire pouvant induire ou aggraver par elle-même l'hyper immunisation. Cette prise en charge doit se justifier au cas par cas dans le dossier médical du patient.

Effet du rituximab dans la prévention du rejet de greffe cardiaque

Auteur principal	Type d'étude	Posologie	Suivi	Critères d'évaluation	Résultats
Bucin (2006)	Cas clinique n=1 -D/R : A/0 - AC antiHLA spécifiques du donneur +	Rituximab 375 mg/m² + MMF, FK506, prednisone, + Ig IV + immuno-adsorption	2 ans	Survenue de rejet Titre Ac anti-A Titre Ac anti-HLA spécifiques du donneur	- Pas de rejet hyperaigu -Titre Ac anti-HLA spécifiques du donneur : ↓ de 128 à 16 post-tt - Titre Ac-anti A1 : ↓ de 256 à 0 post-tt - Crossmatch : toujours positif à 6 mois ; test de lymphocytotoxicité non modifié à 6 mois - Titre Ac anti-HLA DQ3 fortement réactifs Titre Ac anti-HLA DR4 et B62 : négativation Titre Ac anti-HLA A24 : diminution IgM anti-A1: disparition à 1 an ; IgG anti-A1 : persistance à faible titre (de 1 à 2)

Bibliographie

1-Garrett HE Jr, Groshart K, Duvall-Seaman D, Combs D, Suggs R Treatment of humoral rejection with rituximab. Ann Thorac Surg. 2002 Oct;74(4):1240-2

2-Aranda JM Jr, Scornik JC, Normann SJ, Lottenberg R, Schofield RS, Pauly DF, Miles M, Hill JA, Sleasman JW, Skoda-Smith S. Anti-CD20 monoclonal antibody (rituximab) therapy for acute cardiac humoral rejection: a case report.Transplantation. 2002 Mar 27;73(6):907-10.

3-Baran DA, Lubitz S, Alvi S, Fallon JT, Kaplan S, Galin I, Correa R, Courtney MC, Chan M, Spielvogel D, Lansman SL, Gass AL. Refractory humoral cardiac allograft rejection successfully treated with a single dose of rituximab.Transplant Proc. 2004 Dec; 36(10):3164-6.

4-Garrett HE Jr, Duvall-Seaman D, Helsley B, Groshart K. Treatment of vascular rejection with rituximab in cardiac transplantation. J Heart Lung Transplant. 2005 Sep; 24(9):1337-42.

5-Heart transplantation across antibodies against human leukocyte antigen and ABO-post-transplant follow-up of donor reactive antibodies. Bucin D, Johansson S, Lindberg LO. Xenotransplantation. 2006 Mar;13(2):101-4.

Résumé-abstract

Garrett HE Jr, Groshart K, Duvall-Seaman D, Combs D, Suggs R. Treatment of humoral rejection with rituximab. Ann Thorac Surg. 2002 Oct;74(4):1240-2.

Humoral vascular rejection is a B cell-mediated production of immunoglobulin G antibody against the transplanted organ. Available treatments of vascular rejection offer limited success, and chronic manifestations of vascular rejection require retransplantation. On the basis of the mechanism of action of rituximab, we successfully treated 1 patient with vascular rejection refractory to plasmapheresis with this drug without major toxicity.

Aranda JM Jr, Scornik JC, Normann SJ, Lottenberg R, Schofield RS, Pauly DF, Miles M, Hill JA, Sleasman JW, Skoda-Smith S. Anti-CD20 monoclonal antibody (rituximab) therapy for acute cardiac humoral rejection: a case report. Transplantation. 2002 Mar 27;73(6):907-10.

Humoral or antibody-mediated rejection in cardiac transplant recipients is mediated by donor-specific cytotoxic antibodies and is histologically defined by linear deposits of immunoglobulin and complement in the myocardial capillaries. Antibody-mediated rejection often is accompanied by hemodynamic compromise and is associated with reduced long-term graft survival. Standard immunosuppression, designed to target T cell immune function, is largely ineffective against this B cell-driven process. Current treatment options for humoral rejection are limited by a lack of specific anti-B cell therapies. We present the case of a 50-year-old woman with hemodynamically significant humoral rejection resistant to steroids, cyclophos-phamide, and plasmapheresis who responded to the addition of anti-CD20 monoclonal antibody therapy (rituximab). One year posttransplant, the patient is rejection-free, with normal left ventricular systolic function and coronary arteries.

Baran DA, Lubitz S, Alvi S, Fallon JT, Kaplan S, Galin I, Correa R, Courtney MC, Chan M, Spielvogel D, Lansman SL, Gass AL. Refractory humoral cardiac allograft rejection successfully treated with a single dose of rituximab. Transplant Proc. 2004 Dec; 36(10):3164-6.

Despite improvements in immunosuppression over the last two decades, the risk of allograft rejection is still high in the early postoperative period. Cellular rejection accounts for the majority of these episodes. However, humoral rejection is a distinct phenomenon that carries a high rate of graft loss and mortality. The currently available treatments for this serious clinical problem include anti-lymphocyte antibodies, immune globulin infusions, as well as plasmapheresis, all of which have limitations. We describe a case of refractory humoral cardiac rejection successfully treated with a single dose of rituximab (375 mg/m2). No further episodes occurred with 2 years of follow-up.

Garrett HE Jr, Duvall-Seaman D, Helsley B, Groshart K. Treatment of vascular rejection with rituximab in cardiac transplantation. J Heart Lung Transplant. 2005 Sep; 24(9):1337-42.

BACKGROUND: Vascular rejection is the B-cell-mediated production of immunoglobulin G (IgG) antibody against the transplanted heart. The currently available treatments for vascular rejection have had limited success, and chronic manifestations of vascular rejection require re-transplantation. Rituximab is a monoclonal antibody directed against the CD20 receptor of B-lymphocytes, which is approved for treatment of lymphoma. METHODS: Vascular rejection was defined as positive immunofluorescent endomyocardial biopsy staining for IgG and complement, 25% reduction in left ventricular ejection fraction (LVEF) from baseline, and absence of cellular rejection. Over the last 3 years, 8 patients with vascular rejection were treated with intravenous rituximab at a dose of 375 mg/m2 per week for 4 weeks. RESULTS: All patients had normal LVEF post-transplant (average 58%), but developed left ventricular dysfunction (average decrease of 43%) associated with endomyocardial biopsy evidence of vascular rejection. Post-treatment, LVEF returned to baseline (average 53%) with complete resolution of immunofluorescent staining by endomyocardial biopsy. No patient suffered significant infection or drug-related complications. CONCLUSIONS: Rituximab is beneficial for treatment of vascular rejection. Further study is indicated to verify the safety, efficacy and mechanism of action of rituximab therapy for vascular rejection.

Bucin D, Johansson S, Lindberg LO.Heart transplantation across antibodies against human leukocyte antigen and ABO-post-transplant follow-up of donor reactive antibodies. Xenotransplantation 2006 Mar;13(2):101-4.

BACKGROUND: We have successfully performed heart transplantation despite the most unfavourable risk factors for graft and patient survival: the presence of a high level of antibodies (Abs) against the donor's human leukocyte antigens (HLA) class I/II and blood group A1 antigens. The present study concerns post-transplant follow-up and characterization of donor reactive antibodies (DRA). METHODS: Pre-transplant treatment consisted of mycophenolate mofetil (MMF), prednisolone, tacrolimus, intravenous immunoglobulin (IVIG), rituximab, protein-A immunoadsorption (PAIA) and per-operative plasma exchange. A standard triple-drug immunosuppressive protocol was used post-operatively. Abs were analyzed by the complement dependent cytotoxicity (CDC) test against donor and panel B/T cells and by flow cytometry (FlowPRA tests detecting isolated HLA class I/II antigens). Abs against the donor's erythrocytes were analyzed using a standard direct agglutination test for immunoglobulin M (IgM) Abs and a Bio-Rad AHG gel card test detecting IgG Abs and C3d. RESULTS: Pre-transplant treatment reduced Ab titers against the donor's lymphocytes from 128 to 16 and against the donor's blood group A1 antigen from 256 to 0. The patient was

emergently transplanted with a heart from a blood group incompatible donor (A1 secretor to O). No hyperacute rejection was seen. DRA were present against all mismatched HLA class I and class II antigens at the time of transplantation; two of these DRA Abs disappeared within the first year post-transplant (anti-B62 and anti-DR4), one showed weakened reactivity (anti-A24) and one is still strongly reactive (anti-DQ3). The donor-specific CDC cross-match is still positive (titers 2 to 8). The level of panel reactive antibodies (PRA) remained unchanged from 6 months on post-transplant. Rising anti-A1 blood group Abs preceded the second rejection and were adsorbed by two blood group specific immunoadsorptions (Glycosorb)-ABO) and remained at a low level. IgM anti-A1 blood group Abs disappeared at 1 yr post-transplant and IgG Abs are still reactive with blood group A1 erythrocytes but at low titers (1 to 2). CONCLUSIONS: The patient is clinically well 2 years after heart transplantation despite the constant persistence of donor reactive IgG Abs against blood group A1 and HLA-DQ antigens. The reactivity of DRA against other mismatched HLA antigens disappeared or weakened during the follow-up period

---

- **Traitement préventif et curatif du rejet de greffe rénale**

Dans le cadre d'une association aux IgIV et aux échanges plasmatiques, une triple prescription pourrait se justifier pour agir sur les éléments suivants :

- IgIV pour lutter contre les Ac présents,
- échanges plasmatiques pour éliminer les anticorps présents,
- rituximab pour inhiber la resynthèse d'anticorps.

Un PHRC dans la greffe rénale est actuellement en cours : Impact d'un traitement par le rituximab sur l'évolution des rejets aigus humoraux après transplantation rénale : CHU de Tours, Investigateur principal: Pr Lebranchu.

Aucun schéma posologique n'est défini. Par analogie avec les données publiées, une posologie de 375 mg/m² est habituellement retenue. La fréquence des injections n'est pas clairement définie et se situe au minimum à 2 et au maximum à 4 injections à une semaine d'intervalle.

Traitement préventif du rejet de greffe rénale

Il existe 2 types de situation :

- Le traitement préventif du rejet en cas de greffe rénale ABO incompatible. Cette situation ne saurait être prise en compte dans notre pays où la greffe ABO incompatible n'est pas autorisée. Elle est donc réglementairement inacceptable et il faut noter que la majorité des publications sur le sujet concerne cette situation.

- La réduction du taux d'anticorps anti-HLA chez des patients hyperimmunisés dont l'accès à la greffe est très difficile en transplantation cadavérique mais également en cas de greffe avec donneur vivant.
  Le rationnel est qu'une déplétion B-lymphocytaire permettrait de réduire le taux d'anticorps et de permettre de négativer des crossmatch.
  La seule étude publiée dans cette situation est une étude de phase 1 montrant qu'après une injection de rituximab, 7 patients sur 2 ont vu leur taux d'anticorps diminuer de façon plus ou moins importante ou ont vu disparaître certaines spécificités anti-HLA.

  Sur ces seuls éléments, il semble difficile de recommander l'utilisation du rituximab en dehors d'un essai ou d'un protocole.
  Par ailleurs, se posent les modalités de son association avec le traitement plus largement utilisé qui comporte des échanges plasmatiques, des immunoglobulines intra-veineuses et plus ou moins une splénectomie.

Effet du rituximab dans la prévention du rejet de greffe rénale

Auteur principal	Type d'étude	Posologie	Suivi	Critères d'évaluation	Résultats
Vieira (2004)	**Essai phase I n=9** Ac anti HLA + Patients en attente de greffe rénale	Rituximab: - groupe 1 : n=3 ; 50 mg/m² en dose unique - groupe 2 : n=3 ; 150 mg/m² en dose unique ; - groupe 3 : n=3 ; 375 mg/m²	1 an	Marqueurs de surface cellulaires Test de lymphocytotoxicité	- Test de lymphocytotoxicité : inchangé : n=2/9 ; architecture de l'histogramme modifiée : n=5/9, - Négativation du crossmatch : n=1 - A J2 (par rapport à préRTX) : déplétion en cellules CD19+ (p<0.001) et en cellules CD20+ (p<0.001), <u>Tolérance</u> : Infection à histoplasmose (n=1) + infections sur KT de dialyse (n=2), fièvre (n=1)

<u>Traitement curatif du rejet de greffe rénale</u>

La littérature fait état de 2 cas anecdotiques rapportés et d'une petite étude rétrospective de cohorte chez 27 patients. Ces 3 publications posent le même problème de la définition du rejet aigu vasculaire résistant au traitement classique associant corticoïdes, ATG (Anti-Thymocytes Globulin) ou OKT3 (muromonab).

- Alausa et al. publient un cas dans lequel, après 6 jours d'ATG, le rituximab a été introduit en même temps que l'OKT3. Il est donc impossible de savoir lequel de ces 2 médicaments a permis d'obtenir une amélioration.

- Dans l'étude de Lehnardt, le rituximab a été administré après bolus de corticoïdes puis ATG sans biopsie de contrôle réalisée après l'ATG. Il est donc impossible d'affirmer que c'est le rituximab qui a permis d'obtenir une amélioration
  Par ailleurs, dans ce cas, un syndrome lympho-prolifératif est survenu dans les suites, justifiant la poursuite du rituximab.

- L'étude rétrospective de Becker chez 27 patients a étudié l'effet d'une injection de rituximab administrée en association à des corticoïdes, de l'ATG et des échanges plasmatiques. L'indication du rituximab n'était pas basée sur des critères histologiques mais sur des critères purement cliniques : une créatinémie qui ne diminuait pas dans les 48 h suivant le traitement conventionnel. Or d'une part, il est connu que le délai pour obtenir une amélioration de la fonction rénale peut dépasser 48 h sans autre intervention. D'autre part, concernant l'évolution à terme, il est noté 6 décès (22%) et en tout, 9 pertes de greffon (33%). Ces résultats ne semblent pas meilleurs que ceux obtenus dans la littérature avec le traitement conventionnel des rejets vasculaires.

Effet du rituximab dans le traitement curatif du rejet de greffe rénale

Auteur principal	Type d'étude	Posologie	Suivi	Critères d'évaluation	Résultats
Becker (2004)	**Série de cas n=27**	Rituximab 1 dose 375 mg/m² + corticoïdes (n=24) +plasmaphérèse et Ig anti-thymocyte (n=22)	605 jours +/-335.3	Créatininémie Survie du greffon	↓ créatininémie de 5.6 +/- 1.0 mg/dl lors du rejet à 0.95 +/-0.7 mg/dl pour les 24 répondeurs Perte du greffon : n=3 <u>Tolérance :</u> - Décès : n=6 : 4 à plus de 90 jours post-rituximab (sepsis, arrêt respiratoire, crise cardiaque) ; et 2 précoces à J7

Auteur principal	Type d'étude	Posologie	Suivi	Critères d'évaluation	Résultats
					et J28 (IdM, complication chirurgicale avec hémorragie) - Pas de complication hématologique ni PTLD[1] à 2 ans
Alausa (2005)	**Cas clinique n=1**	Rituximab + muromonab	9 mois	Tt rejet initial Fonction rénale	Tt rejet initial Créatininémie : 1.7 mg/dL Absence de récidive de rejet <u>Tolérance :</u> Pas de complications infectieuses
Lehnhardt (2006)	**Cas clinique n=1**	Rituximab 375 mg/m² 1 injection	13 mois	Biospie greffon à J12, J25, J33 et J57post-rituximab Créatininémie	- Biopsie à J5 post-rituximab (J57 post-greffe) : résolution complète du rejet aigu - Créatininémie : de 347µmol/l à J52 à 175 µmol/l à 6 mois et 150 µmol/l à 13 mois. <u>Tolérance</u> : Pas d'infections fongiques ni bactériennes

1. PTLD : post-transplant lymphoproliferative disorder

En conclusion, il n'existe pas d'arguments convaincants permettant de recommander le rituximab ors-AMM dans la prévention ou le traitement curatif du rejet en greffe rénale.

Les situations de sauvetage demanderaient également à être mieux définies.

D'autres situations ont été identifiées mais ne peuvent faire l'objet d'un PTT en l'état actuel des connaissances :
- certaines récidives de maladies sur greffon,
- glomérulonéphrite membrano-prolifération,
- syndrome néphrotique,
- glomérulonéphrite extramembraneuse.

Bibliographie

1-Rituximab for reduction of anti-HLA antibodies in patients awaiting renal transplantation: 1. Safety, pharmacodynamics, and pharmacokinetics.Vieira CA, Agarwal A, Book BK, Sidner RA, Bearden CM, Gebel HM, Roggero AL, Fineberg NS, Taber T, Kraus MA, Pescovitz MD. Transplantation. 2004 Feb 27;77(4):542-8.

2-Rituximab as treatment for refractory kidney transplant rejection.Becker YT, Becker BN, Pirsch JD, Sollinger HW. Am J Transplant. 2004 Jun; 4(6):996-1001

3- Nodular B-cell aggregates associated with treatment refractory renal transplant rejection resolved by rituximab. Lehnhardt A, Mengel M, Pape L, Ehrich JH, Offner G, Strehlau J. Am J Transplant. 2006 Apr; 6(4):847-51.

4- Refractory acute kidney transplant rejection with CD20 graft infiltrates and successful therapy with rituximab. Alausa M, Almagro U, Siddiqi N, Zuiderweg R, Medipalli R, Hariharan S. Clin Transplant. 2005 Feb;19(1):137-40.

Résumés-Abstracts

Vieira CA, Agarwal A, Book BK, Sidner RA, Bearden CM, Gebel HM, Roggero AL, Fineberg NS, Taber T, Kraus MA, Pescovitz MD. Rituximab for reduction of anti-HLA antibodies in patients awaiting renal transplantation: 1. Safety, pharmacodynamics, and pharmacokinetics. Transplantation. 2004 Feb 27;77(4):542-8.

<u>BACKGROUND:</u> Preformed HLA antibodies (Ab), reported as panel-reactive antibody (PRA), prolong patient waiting time for kidney transplantation. We hypothesized that rituximab (RTX) could reduce PRA via B-cell depletion. This initial study reports the safety, pharmacokinetics, and pharmacodynamics of RTX in patients with end-stage renal

failure. METHODS: The study was an investigator-initiated single-dose, dose-escalation phase I trial of RTX in chronic dialysis patients (PRA >50%). It was approved by the Institutional Review Board and the Food and Drug Administration. Nine subjects were treated with a single dose of RTX (n=3 per group) at 50, 150, or 375 mg/m. Peripheral lymphocyte cell surface markers and HLA Ab levels (%PRA and titers) were tested using flow cytometry. RESULTS: There were four significant adverse events: a suspected histoplasmosis infection; two Tenchkoff dialysis catheter infections; and fever (38.7 degrees C) during infusion. At 2 days after RTX therapy, there was depletion of CD19 cells (pre-RTX 181+/-137 vs. post-RTX 12+/-5.6, P =0.006). In 2 (22%) of 9 subjects, there was no appreciable change in PRA. Among the other seven patients, one had a decrease in PRA from 87% to 51% with a concurrent decrease in fluorescence intensity; five patients had changes in histogram architecture suggesting loss of antibody specificity; and one patient had a fourfold decrease in PRA titer from 1:64 to 1:16 at 6 months after treatment. In addition, one of the seven patients converted a donor-specific crossmatch to negative and underwent a successful living donor kidney transplantation. CONCLUSIONS: RTX can be safely administered and may be an effective agent to reduce high-titer anti-HLA Abs in subjects awaiting kidney transplantation.

Becker YT, Becker BN, Pirsch JD, Sollinger HW. Rituximab as treatment for refractory kidney transplant rejection. Am J Transplant. 2004 Jun; 4(6):996-1001

Recent studies have shown that a high density of CD 20+ cells are seen in patients who have steroid-resistant rejection episodes. Rituximab is a high-affinity CD-20 specific antibody that inhibits B-cell proliferation while inducing cellular apoptosis. Thus, it is a rational choice for therapy in transplantation to abrogate B-cell-mediated events. Twenty-seven patients were diagnosed with biopsy-confirmed rejection manifested by thrombotic microangiopathy and/or endothelialitis between 2/99 and 2/02 at our institution. These individuals were treated with a single dose of rituximab, in addition to other therapies, in an effort to reverse their rejection episodes. Twenty-four received additional steroids while 22 of the 27 patients were also treated with plasmapheresis and antithymocyte globulin (ATG). Only three patients experienced graft loss not associated with patient death during the follow-up period (605 +/- 335.3 days). In the 24 successfully treated patients, the serum creatinine at the time of initiating rituximab therapy was 5.6 +/- 1.0 mg/dL and decreased to 0.95 +/- 0.7 mg/dL at discharge. The addition of rituximab may improve outcomes in severe, steroid-resistant or antibody-mediated rejection episodes after kidney transplantation.

Lehnhardt A, Mengel M, Pape L, Ehrich JH, Offner G, Strehlau J. Nodular B-cell aggregates associated with treatment refractory renal transplant rejection resolved by rituximab. Am J Transplant. 2006 Apr; 6(4):847-51.

Acute rejection episodes leading to treatment refractory early graft loss are increasingly rare events in living related renal transplantation today. Pathophysiologic pathways often remain unsolved. We report on tubulointerstitial and vascular rejection developing within 2 weeks after transplantation in a 12-year-old boy treated with cyclosporine, mycophenolate, steroids and double blinded basiliximab. Despite steroid pulses, switch to tacrolimus and ATG serum creatinine peaked at 347 micromol/L with imminent graft loss and ongoing C4d negative cellular vascular rejection. Permanent gain of function was only achieved after a single dose of rituximab. Retrospectively CD20+ nodular B-cell aggregates could be demonstrated in all three biopsies obtained prior to rituximab and resolved concomitantly with functional improvement. Our case for the first time demonstrates resolution of nodular CD20+ infiltrates and decline of OX40, NF-kappaB and CTL transcription shortly after rituximab indicating a B-cell facilitated C4d negative pathway. Single dose rituximab may effectively reverse even long-lasting refractory rejection.

Alausa M, Almagro U, Siddiqi N, Zuiderweg R, Medipalli R, Hariharan S. Refractory acute kidney transplant rejection with CD20 graft infiltrates and successful therapy with rituximab. Clin Transplant. 2005 Feb;19(1):137-40.

Acute rejection is an expected event after transplantation and has been associated with poor long-term kidney transplant outcome. The presence of B cells in the kidney graft with acute rejection is thought to be an omnious sign, as it has been associated with poor graft outcome. There is no definitive treatment for acute rejection with B cells in the graft. Rituximab, a humanized monoclonal antibody against CD20, has been used in the treatment of B cell lymphoma. We present the case of a 49-yr-old Caucasian male with early acute kidney allograft rejection that was refractory to high doses of steroids and rabbit anti-thymocyte globulin (thymoglobulin). Repeat renal biopsy revealed T cell and B cells in the kidney graft and responded to the combination of rituximab and muromonab (a mouse monoclonal antibody to CD3 receptor). Over 9 months post-transplant, the patient remains rejection free with a serum creatinine of 1.7 mg/dL.

- **Traitement du rejet de greffe hépatique**

Il n'existe aucune étude publiée concernant l'utilisation du rituximab dans cette situation.

- **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

BIBLIOGRAPHIE

1- Merrill JT, Neuwelt CM, Wallace DJ, Shanahan JC, Latinis KM, Oates JC, Utset TO, Gordon C, Isenberg DA, Hsieh HJ, Zhang D, Brunetta PG. 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. Arthritis Rheum. 2010 Jan;62(1):222-33.
2- Furie R, Looney R. J, Rovin B., Latinis KM., Appel G., Sanchez-Guerrero J, Fervenza, F.C. Efficacy and Safety of Rituximab in Subjects with Active Proliferative Lupus Nephritis (LN): Results From the Randomized, Double-Blind Phase III LUNAR Study. Arthritis & Rheumatism, Volume 60, October 2009 Abstract. Supplement The 2009 ACR/ARHP Annual Scientific Meeting, Philadelphia October 16-21, 2009.

3-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. Safety and efficacy of rituximab in systemic lupus erythematosus: Results from 136 patients from the French AIR registry. Arthritis Rheum. 2010 May 5.
4-Lu TY, Ng KP, Cambridge G, Leandro MJ, Edwards JC, Ehrenstein M, Isenberg DA. 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. Arthritis Rheum. 2009 Apr 15;61(4):482-7.
5-Catapano F, Chaudhry AN, Jones RB, Smith KG, Jayne DW. Long-term efficacy and safety of rituximab in refractory and relapsing systemic lupus erythematosus. Nephrol Dial Transplant. 2010 May 11.
6-Leandro MJ, Cambridge G, Edwards JC, Ehrenstein MR, Isenberg DA. B-cell depletion in the treatment of patients with systemic lupus erythematosus: a longitudinal analysis of 24 patients. Rheumatology (Oxford). 2005 Dec;44(12):1542-5.
7-Vigna-Perez M, Hernández-Castro B, Paredes-Saharopulos O, Portales-Pérez D, Baranda L, Abud-Mendoza C, González-Amaro R. Clinical and immunological effects of Rituximab in patients with lupus nephritis refractory to conventional therapy: a pilot study.Arthritis Res Ther. 2006;8(3):R83.
8- 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. Rituximab in severe lupus nephritis: early B-cell depletion affects long-term renal outcome. Clin J Am Soc Nephrol. 2009 Mar;4(3):579-87.
9-Pepper R, Griffith M, Kirwan C, Levy J, Taube D, Pusey C, Lightstone L, Cairns T. Rituximab is an effective treatment for lupus nephritis and allows a reduction in maintenance steroids. Nephrol Dial Transplant. 2009 Dec;24(12):3717-23.
10- Looney RJ, Anolik JH, Campbell D, Felgar RE, Young F, Arend LJ, Sloand JA, Rosenblatt J, Sanz I. B cell depletion as a novel treatment for systemic lupus erythematosus: a phase I/II dose-escalation trial of rituximab. Arthritis Rheum. 2004 Aug;50(8):2580-9.
11- Boletis JN, Marinaki S, Skalioti C, Lionaki SS, Iniotaki A, Sfikakis PP. Rituximab and mycophenolate mofetil for relapsing proliferative lupus nephritis: a long-term prospective study. Nephrol Dial Transplant. 2009 Jul;24(7):2157-60.
12- Sfikakis PP, Boletis JN, Lionaki S, Vigklis V, Fragiadaki KG, Iniotaki A, Moutsopoulos HM. 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. Arthritis Rheum. 2005 Feb;52(2):501-13.
13- Marks SD, Patey S, Brogan PA, Hasson N, Pilkington C, Woo P, Tullus K. B lymphocyte depletion therapy in children with refractory systemic lupus erythematosus. Arthritis Rheum. 2005 Oct;52(10):3168-74.
14- 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. Rituximab therapy for childhood-onset systemic lupus erythematosus.J Pediatr. 2006 May;148(5):623-627.
15- Leandro MJ, Edwards JC, Cambridge G, Ehrenstein MR, Isenberg DA. An open study of B lymphocyte depletion in systemic lupus erythematosus. Arthritis Rheum. 2002 Oct;46(10):2673-7.
16- 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). Tolerance and short term efficacy of rituximab in 43 patients with systemic autoimmune diseases. Ann Rheum Dis. 2005 Jun;64(6):913-20.
17- Ramos-Casals M, Diaz-Lagares C, Soto-Cardenas MJ, Brito-Zeron P, Cuadrado MJ, Sanna G, Bertolaccini L, Khamashta MA Rituximab Therapy in Lupus Nephritis: Current Clinical Evidence. Clin Rev Allergy Immunol. 2010 Apr 24.
18- 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. Anti-CD20 therapy in patients with refractory systemic lupus erythematosus: a longitudinal analysis of 52 Hispanic patients. Lupus. 2010 Feb;19(2):213-9.
19- Reynolds JA, Toescu V, Yee CS, Prabu A, Situnayake D, Gordon C. Effects of rituximab on resistant SLE disease including lung involvement. Lupus. 2009 Jan;18(1):67-73.
20- Lateef A, Lahiri M, Teng GG, Vasoo S. Use of rituximab in the treatment of refractory systemic lupus erythematosus: Singapore experience.Lupus. 2010;19(6):765-70.
21- Edelbauer M, Jungraithmayr T, Zimmerhackl LB. Rituximab in childhood systemic lupus erythematosus refractory to conventional immunosuppression: case report. Pediatr Nephrol. 2005 Jun;20(6):811-3.
22- Murray E, Perry M. Off-label use of rituximab in systemic lupus erythematosus: a systematic review. Clin Rheumatol. 2010 Jul;29(7):707-16.
23- Lightstone L. Lupus nephritis: where are we now? Curr Opin Rheumatol. 2010 May;22(3):252-6.
24- Looney RJ. B cell-targeted therapies for systemic lupus erythematosus: an update on clinical trial data.Drugs. 2010 Mar 26;70(5):529-40.
25- Favas C, Isenberg DA. B-cell-depletion therapy in SLE--what are the current prospects for its acceptance?Nat Rev Rheumatol. 2009 Dec;5(12):711-6.
26- Ramos-Casals M, Díaz-Lagares C, Khamashta MA. Rituximab and lupus: good in real life, bad in controlled trials. Arthritis Rheum. 2009 Sep 15;61(9):1281-2. Comment on the article by Lu et al.

27- Looney RJ, Anolik J, Sanz I. A perspective on B-cell-targeting therapy for SLE. Mod Rheumatol. 2010 Feb;20(1):1-10.
28- 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. Use of rituximab in patients with systemic lupus erythematosus: an update.Autoimmun Rev. 2009 Feb;8(4):343-8.

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.