EXTENDED REPORT

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

J-E Gottenberg, L Guillevin, O Lambotte, B Combe, Y Allanore, A Cantagrel, C Larroche, M Soubrier, L Bouillet, M Dougados, O Fain, D Farge, X Kyndt, O Lortholary, C Masson, B Moura, P Remy, T Thomas, D Wendling, J-M Anaya, J Sibilia, X Mariette, for the Club Rhumatismes et Inflammation (CRI)

Ann Rheum Dis 2005;**64**:913–920. doi: 10.1136/ard.2004.029694

See end of article for authors' affiliations

Correspondence to: Professor Xavier Mariette, Service de Rhumatologie, Hôpital de Bicêtre, 78 rue du Général Leclerc, 94275 Le Kremlin Bicêtre, France; xavier.mariette@bct.ap-hop-paris.fr

Accepted 9 November 2004
Published Online First 18 November 2004

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 email 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 Sjögren'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.

After decades during which the T cell was considered the cornerstone of autoimmunity, interest has recently grown in the pivotal role of B cells in autoantibody secretion, autoantigen presentation,[1] proinflammatory cytokine production,[2] and regulation of dendritic cell function.[3] Thus rituximab, a chimeric monoclonal antibody specific for human CD20, which targets B lymphocytes, could be a potential new biological treatment for autoimmune diseases. To date, rheumatoid arthritis is the only disease in which the efficacy of rituximab has been demonstrated in a controlled trial.[4] Because rituximab has received marketing authorisation for lymphoma, and despite the absence of marketing authorisation in autoimmune disorders, some clinicians have already started to use it to treat refractory autoimmune diseases.

The Club Rhumatismes et Inflammation (CRI), a section of the Société Française de Rhumatologie, has 866 members from approximately 100 departments of rheumatology and internal medicine registered on its web site, which allows the collection of reliable data on practice in France with respect to autoimmune diseases. The present retrospective study was initiated by the CRI to evaluate the safety and efficacy of rituximab in patients with diverse autoimmune diseases.

METHODS

Patient selection

Eight hundred and sixty six rheumatology and internal medicine practitioners registered on the CRI web site were contacted four times by email to obtain the files of patients treated with rituximab for the following systemic autoimmune diseases: rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), primary Sjögren's syndrome (pSS), and vasculitis. The files were reviewed by two of us (XM and JEG). The diagnoses were reassessed using the international consensus criteria (American College of Rheumatology for RA, SLE, and vasculitis, and the European–American consensus group criteria for pSS). Patients with lymphoma were analysed if the evolution of the autoimmune disease could be evaluated.

Treatment

The number of rituximab infusions, the dosage, and the timing of the infusions were recorded in each patient. Concomitant drugs, including immunosuppressant agents and prednisone, were noted.

Assessment

Tolerance and adverse events were recorded for each patient. The 28 joint disease activity score (DAS28) and the SLE disease activity index (SLEDAI) values were recorded in patients with RA and SLE, respectively. In patients with RA or SLE, efficacy was defined as a decrease of 50% (partial remission) or more of the initial DAS28 and SLEDAI values,

Abbreviations: ACR, American College of Rheumatology; ANCA, antineutrophil cytoplasmic antibodies; DAS28, 28 joint disease activity score; MALT, mucosa associated lymphoid tissue; MC, mixed cryoglobulinaemia; pSS, primary Sjögren's syndrome; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SLEDAI, SLE disease activity index

respectively. Patients with RA and a DAS value below 2.6 were considered to be in complete remission, as were patients with SLE and an SLEDAI value between 0 and 2. In patients with other autoimmune diseases, efficacy was defined as a decrease of 50% (partial remission) or more of the initial disease activity according to the clinician in charge of the patient. Patients with other autoimmune diseases in whom all symptoms and clinical features disappeared were considered to be in complete remission.

RESULTS

Patient characteristics

Twenty four departments of rheumatology and internal medicine had patients treated with rituximab for autoimmune diseases. Forty nine observations were collected. Six were excluded because of diagnostic uncertainty (n = 3) or inability to evaluate the course of the autoimmune disease in patients with lymphoma (n = 3). Thus 43 observations could be analysed. The clinical characteristics of the 43 patients are given in tables 1–5. The study included 14 patients with RA, 13 with SLE, six with pSS, five with systemic vasculitis, and five with other inflammatory arthritides (two with antisynthetase syndrome, one with systemic sclerosis, one with Still's disease, and one with sarcoidosis). Rituximab was prescribed for lymphoma associated with autoimmune disease 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. Nine patients with RA had previously been treated with anti-TNF, seven SLE patients with cyclophosphamide, two patients with type II mixed cryoglobulinaemia with interferon and ribavirin, and three patients with vasculitis had not responded to cyclophosphamide and infliximab.

Characteristics of rituximab administration and concomitant drugs

Thirty five patients received weekly infusions of 375 mg/m^2 of rituximab for four weeks, five patients were given two infusions of 1000 mg, and a different dosage regimen was followed in three patients (cases 3, 5 and 38; tables 1 and 4). Rituximab was given in combination with methotrexate in six patients, and with other immunosuppressants in 15 patients, with pulses of methylprednisolone in seven patients and prescribed alone in 15 (tables 1–5). The mean follow up period was 8.3 months (range 2 to 26).

Tolerance and safety

Eleven adverse events were observed in 10 patients. Infusion related reactions, such as transient hypotension or hypertension, were observed in three patients (cases 10, 33, and 35). These reactions occurred during the first infusion in two patients (cases 10 and 33), who had experienced previous infusion related reactions with infliximab, and during the seventh infusion (the third after a clinical relapse) in the other (case 35). In one patient with chronic hepatitis C (patient 34) and renal function impairment (creatinine clearance 35 ml/min), two repeated episodes of encephalopathy developed two days after the second and third infusion, concomitantly with hyperammonaemia (2.18 and 4.17 mg/l, respectively; normal <0.8 mg/l). This patient had histological features of chronic hepatitis, without cirrhosis. Two patients with SLE (cases 22 and 24) and one with pSS (case 29) had serum sickness-like reactions (urticaria and arthralgias within two days of the first and third infusions (case 22), fever, urticaria, and arthralgias after the second, third, and fourth infusions (case 24), and after the second and third (last) infusions (case 29). These serum sickness-like reactions were moderate and led to treatment discontinuation in one patient only (case 29). In one patient with SLE

Table 1 Demographic, clinical, and biological data on 14 patients treated with rituximab for rheumatoid arthritis

Case	Sex/age/duration of disease (y)	No of prior DMARD/prior anti-TNF (Y/N)	Non-articular involvement (Y/N)	No of infusions × dose (mg)/No of MP pulses/ concomitant IS	Adverse event (Y/N)	Efficacy RA/non-articular involvement (Y/N)	Time to response (w)/follow up (m)	DAS28 initial/last†	Prednisone initial/last‡ (mg/d)	RF initial/last (IU/ml) (n <20)	Relapse (Y/N)/ time to relapse (m)
1	F/48/4	8/Y	N	4×375.m^{-2}/HQ	N	Y	4/6	5.9/2.9	15/10	Pos/NA	N
2	M/83/3	3/Y	Y/lymph	4×375.m^{-2}/4/MP (100)	N	Y/Y	6/5.5	7.6/2.4	12/9	NA	Y/5.5
3	F/42/15	11/Y	N	27×375.m^{-2}/MTX,CPH	N	Y	16/15	8.3/3.6	10/10	270/150	Y/5
4	F/47/2	4/Y	N	2×1000/2/MP (100)/MTX+HQ	N	Y	4/3	8.7/4.7	0/0	240/122	N
5	F/68/18	3/N	Y/lymph	8×1000/8/CHOP	N	Y/Y	4/24	5.3/2.7	3/0	266/20	N
6	M/57/7	3/Y	N	2×1000/CPH	N	Y	4/5	6/3.2	20/10	938/441	N
7	F/41/8	5/Y	N	2×1000/MTX	N	N	–/4	6/5.2	10/10	95/NA	–
8	M/55/12	6/Y	N	2×1000	N	Y	4/8	7.9/3.6	17.5/10	Pos/neg	N
9	F/48/7	5/N	N	2×1000/MTX	N	Y	8/12	4/1.8	10/2.5	Neg/neg	
10	M/49/3	7/Y	N	1×375.m^{-2}/1/MP (100)	Infusion related	N	–/3	NA	10/10	Pos/pos	–
11	F/68/34	5/Y	N	4×375.m^{-2}/4/MP (40)	N	Y	4/3	6.6/3.8	4/4	NA	N
12	F/53/3	2/N	N	4×375.m^{-2}/4/MP (40)	N	Y	6/6	6.5/2.2	4/0	20/20	N
13*	M/67/2	1/N	Y/Felty	4×375.m^{-2}	N	N/N	–/6	6.6/6.7	15/15	Neg/neg	–
14*	M/53/4	2/N	Y/Felty	4×375.m^{-2}/MTX	N	Y/N	4/12	7.5/2.1	15/10	60/14	N

*Evolution of neutropenia in patients 13 and 14 was described in a submitted case report.
†p<0.0002 between DAS28 value pre- and post-treatment using paired *t* test.
‡p<0.01 between prednisone dose pre- and post-treatment.
CPH, cyclophosphamide; DAS28, 28 joint disease activity score; DMARD, disease modifying antirheumatic drug; F, female; HQ, hydroxychloroquine; IS, immunosuppressants; lymph, lymphoma; m, months; M, male; MP, methylprednisolone; MTX, methotrexate; N, no; NA, not available; neg, negative; pos, positive; RA, rheumatoid arthritis; RF, rheumatoid factor (determined by nephelometry, except where stated "pos/neg", when determined by latex); TNF, tumour necrosis factor; w, weeks; y, years; Y, yes; –, not relevant.

Table 2 Demographic, clinical, and biological data on 13 patients treated with rituximab for systemic lupus erythematosus

Case	Sex/age/ duration (y)	No of prior IS/prior CPH (Y/N)	Clinical involvement	No of infusions × dose (mg)/No of MP pulses/ concomitant IS	Adverse event (Y/N)	Efficacy (Y/N)	Time to response (w)/ follow up (m)	SLEDAI initial/ last†	Prednisone initial/last (mg/d)‡	Anti-dsDNA IgG initial/last ELISA (IU/ml) (n <20)	C3 and/or C4 normalisation (Y/N)	Relapse (Y/N)/ time to relapse (m)
15	F/30/3	1/N	Pleuropericarditis	$1\times375.m^{-2}$	Neutropenia	N	–/6	8/6	25/25	40/neg*	N	–
16	M/20/7	3/Y	Nephritis/myocarditis/Evans	$4\times375.m^{-2}$	N	Y	2/15	18/6	60/10	144/10*	Y	Y/15
17	F/55/8	2/N	Autoimmune haemolytic anaemia, lymphadenopathy	$4\times375.m^{-2}$/2/MP (80)/ ivIg	N	Death	–/2	8/NA	60/15	Neg/neg	N	–
18	M/21/3	2/Y	CNS (psychosis)	$4\times375.m^{-2}$	N	Y	12/26	9/2	50/2	25/neg*	Y	N
19	F/26/10	3/N	Skin, articular	$4\times375.m^{-2}$	N	Y	4/6	6/0	30/6	99/0	Y	N
20	F/41/5	2/N	Articular	$4\times375.m^{-2}$/AZA	N	Y	1/7	6/2	5/2	Neg/neg	NA	N
21	F/30/13	3/Y	Articular, vasculitis, nephritis	$4\times375.m^{-2}$/HQ	Deep vein thrombosis	N	–/5	28/20	50/15	100–500	N	–
22	F/28/19	2/Y	Skin, articular	$4\times375.m^{-2}$	Serum sickness, pulmonary embolism	Y	4/4	6/2	14/13	1280–320	N	N
23	M/33/9	5/Y	Autoimmune thrombocytopenia, nephritis	$4\times375.m^{-2}$/CIC	N	Y	8/9	8/2	30/10	NA/31	Y	Y/9
24	F/28/18	3/N	Autoimmune thrombocytopenia, APS	$3\times375.m^{-2}$/AZA	Serum sickness	Y	4/10	3/2	30/10	300/286	N	N
25	F/28/2	3/Y	Nephritis, thrombotic microangiopathy	$4\times375.m^{-2}$/plasmaph/ CPH	N	Death	–/2	24/NA	60/60	113/NA	N	–
26	F/22/3	3/Y	Articular	$4\times375.m^{-2}$/2/MP (80)/ MMF	Neutropenia	Y	6/7	9/0	12.5/10	199/neg	Y	N
27	F/30/20	2/N	Articular, vasculitis	4×375 ms	N	Y	4/4	18/14§	9/8	50/75	N	N

*Farr's test (n <7).
†p<0.0002 between SLEDAI value pre- and post-treatment using paired *t* test.
‡p<0.01 between prednisone dose pre- and post-treatment.
§Marked improvement in digital angiitis was observed and proteinuria resolved.
APS, antiphospholipid syndrome; AZA, azathioprine; CIC, ciclosporine; CNS, central nervous system; CPH, cyclophosphamide; ELISA, enzyme linked immunosorbent assay; F, female; HQ, hydroxychloroquine; IS, immunosuppressants; ivIg, intravenous immunoglobulin; m, months; M, male; MMF, mycophenolate mofetil; MP, methylprednisolone; MTX, methotrexate; N, no; NA, not available; neg, negative; plasmaph, plasmapheresis; pos, positive; SLEDAI, SLE disease activity index; w, weeks; y, years; Y, yes; –, not relevant.

related end stage renal disease requiring haemodialysis (case 15), a severe sepsis-like syndrome along with neutropenia (blood neutrophil count 0.6×10^9/l) developed 10 days after a 500 mg infusion of rituximab. One patient with SLE had neutropenia (blood neutrophil count 0.7×10^9/l) 15 days after the first infusion of rituximab (case 26). Mycophenolate mofetil, which had been given concomitantly (at a dose of 1.5 g/day), was discontinued and the blood neutrophil count returned to the normal range. Two patients with SLE, including one with nephrotic syndrome (case 21), developed deep vein thrombosis, with pulmonary embolism in one (case 22), five and four months, respectively, after treatment with rituximab. Both patients had IgG anticardiolipin antibodies.

Treatment was discontinued in six of these 11 patients. Late onset neutropenia and marked hypogammaglobulinaemia were not observed, but serum gammaglobulin levels were monitored in only 21 patients. Liver enzyme levels were initially increased above normal by 1.5-fold and twofold in two patients with hepatitis C viral (HCV) replication (cases 34 and 35) and did not change significantly after rituximab treatment. Liver enzyme levels remained within the normal range in the other patients.

Short term efficacy of anti-CD20 treatment

Efficacy of rituximab was observed in 30 patients (70%), including 11 with RA, nine with SLE, five with pSS, two with vasculitis, two with antisynthetase syndromes, and one with sarcoidosis. Efficacy was observed in 17 patients not being treated concomitantly with disease modifying antirheumatic drugs (DMARDs) or immunosuppressants, in five who were also receiving methotrexate, and in eight who were also receiving other DMARDs/immunosuppressants. Mean time to response was 5.4 weeks (range 1 to 16). The mean decrease in daily corticosteroid dose was 9.5 mg (range 0 to 50) in patients who responded to rituximab. Oral corticosteroids could be discontinued in four patients (cases 5, 12, 31, and 33). Seven patients, including five treated with rituximab alone (cases 2, 16, 35, 39, and 41) and two treated with methotrexate and ciclosporine (cases 3 and 23, respectively), experienced relapse after 8.1 months on average (range 5 to 15). Four patients were retreated with rituximab, but the current follow up is insufficient to evaluate the clinical evolution in these patients.

Three patients died because of refractory autoimmune disease (rheumatoid vasculitis, refractory autoimmune haemolytic anaemia in a patient with SLE, and refractory cerebral vasculitis in another SLE patient).

Patients with RA (table 1)

Eleven of 14 patients with RA responded to rituximab, including four who went into complete remission (DAS28 <2.6) and seven who were in partial remission (a decrease of 50% or more of the initial DAS28). The mean (SD) DAS28 decreased from 6.7 (1.3) (range 5.3 to 8.7) to 3.4 (1.4) (range 1.8 to 6.7) ($p<0.0002$, using the paired *t* test). In 11 responders, the mean daily dose of prednisone decreased from 9.3 mg (range 0 to 20) to 5.9 mg (range 0 to 10) ($p<0.01$) after a mean follow up duration of 8.6 months (range 2 to 24). Rheumatoid factor values, evaluated in eight rheumatoid factor (RF) positive patients, decreased in six (table 1).

Patients with SLE (table 2)

Nine of 13 patients with SLE responded to rituximab, including seven who went into complete remission (SLEDAI value between 0 and 2) and two who were in partial remission (a decrease of 50% or more of the initial SLEDAI). Two patients died because of the refractory character of the autoimmune disease. Two of the four SLE

Table 3 Demographic, clinical, and biological data on six patients treated with rituximab for primary Sjögren's syndrome

Case	Sex/age/ duration (y)	Previous IS	Clinical involvement at beginning of rituximab treatment	No of infusions × dose (mg)/No of MP pulses/ concomitant IS	Adverse event (Y/N)	Efficacy on extraglandular involvement (Y/N)	Initial/final VAS	Efficacy on objective dryness (Y/N)	Time to response (w)/ follow up (m)	Prednisone initial/last	RF (IU/l) inial/last (n <20)	Relapse (Y/ N)/time to relapse (m)
28	F/58/15	HQ	Digestive lymphoma (MALT)	$4\times375.m^{-2}$/4/MP (500)/HQ	N	Y	Dryness VAS: 80/50	Stable Schirmer	4/6	9/6	44/0	N
29	F/43/4	No	Salivary lymphoma (MALT)	$4\times375.m^{-2}$	Serum sickness	N	NA	NA	–/11	0/0	499/423	–
30	F/71/5	HQ/CPH/AZA	Vasculitis	$4\times375.m^{-2}$	N	Y	NA	Stable Schirmer, salivary flow =0	8/8	15/7.5	RF: 109/57 cryo: 1%/neg	N
31	F/58/2	CPH	Vasculitis	$4\times375.m^{-2}$	N	Y	NA	NA	8/8	10/0	RF: 170/neg cryo: pos/neg	N
32	F/74/18	MTX/ETA/inflix	Parotid gland enlargement, polysynovitis	$4\times375.m^{-2}$/4/MP (40)	N	Y	Dryness VAS: 60/20 Fatigue VAS: 70/0	NA	4/7	6/6	RF: 130/NA	N
33	F/41/8	CPH	Parotid gland enlargement, polyarthralgia	$2\times375.m^{-2}$/2/MP (40)	Infusion related	Y	Dryness VAS: 20/0 Fatigue VAS: 80/0	NA	4/7	4/0	NA	N

AZA, azathioprine; CPH, cyclophosphamide; cryo, cryoglobulinaemia; ETA, etanercept; F, female; HQ, hydroxychloroquine; inflix, infliximab; IS, immunosuppressants; m, months; M, male; MALT, mucosa associated lymphoid tissue; MP, methylprednisolone; MTX, methotrexate; N, no; NA, not available; neg, negative; pos, positive; RF, rheumatoid factor (determined by nephelometry, except RF stated as ''pos/neg'', determined by latex); VAS, visual analogical scale; w, weeks; y, years; Y, yes; –, not relevant.

patients with active nephritis and seven of the nine without nephritis responded to rituximab. The mean (SD) SLEDAI value decreased from 11 (7) (range 3 to 28) to 5 (6) (range 0 to 20) in the 11 surviving patients ($p<0.0002$, using the paired *t* test). For the nine responders, the mean daily dose of prednisone decreased from 27 mg (range 5 to 60) to 8 mg (range 2 to 13) ($p<0.01$), after a mean follow up duration of 9.8 months (range 4 to 26). The variation in the level of anti-double-stranded DNA antibody was different in individual patients (table 2).

Patients with pSS (table 3)

The efficacy of rituximab and partial remission were observed in five of six patients, with regression of parotid swelling, articular involvement, subjective dryness, and fatigue in two (cases 32 and 33), improvement in subjective dryness in one (case 28), and major improvement in cryoglobulinaemia related vasculitis in two (cases 30 and 31), with concomitant disappearance of cryoglobulinaemia. In one patient with a salivary lymphoma of the MALT subset (case 29), treatment with rituximab was not successful. With respect to glandular symptoms, self reported dryness was improved in only three patients (cases 28, 32, and 33) and was not changed in the three others, whereas objective ocular and mouth dryness, assessed in only cases 28 and 30, was not improved. RF levels decreased in the three responders in whom it was assessed but did not decrease in the patient who was a non-responder to rituximab (table 3). In all patients with anti-SSA/SSB antibodies (four with anti-SSA antibody and two with anti-SSB) these autoantibodies remained detectable after rituximab.

Patients with vasculitis (table 4)

Efficacy of rituximab was observed in two of the five patients in whom partial remission was obtained. One patient with rheumatoid vasculitis died from acute respiratory distress syndrome six weeks after starting on rituximab; this was not caused by alveolar haemorrhage (case 36). In one patient with cirrhosis treated with rituximab for HCV related type II mixed cryoglobulinaemia, skin ulcers healed and there was no detectable cryoglobulinaemia five months after the last infusion (case 35). Peripheral nerve and renal involvement remained stable despite rituximab. The mixed cryoglobulinaemia reappeared seven months after the last infusion of rituximab, and the patient experienced a clinical relapse (purpura flares) five months later. One patient with Wegener's granulomatosis (case 38), who had been a non-responder to methotrexate and mycophenolate mofetil (MMF), experienced a marked response to rituximab: ear, nose and throat involvement was stabilised, and a concomitant pyoderma gangrenosum was markedly improved. Anti-proteinase 3 antibody, determined by enzyme linked immunosorbent assay (initial serum level 90 IU), disappeared within six months of treatment.

Patients with other inflammatory arthritides (table 5)

Polymyositis was greatly improved in two patients treated with rituximab for antisynthetase syndrome (cases 39 (partial remission) and 40 (complete remission)). The creatine kinase (CK) level in case 39 decreased from 252 to 119 IU/l (normal <150). This patient, treated with rituximab alone, also experienced good improvement of pemphigus associated lesions: mucosal lesions disappeared and skin lesions were markedly reduced. The CK level of case 40 decreased from 1364 to 93 IU/l (normal <160) and serum aldolase decreased from 25 to 8 (normal <7.5). Muscle strength normalised in this patient, allowing a marked decrease in daily prednisone. The patient was able to go

Table 4 Demographic, clinical, and biological data on five patients treated with rituximab for systemic vasculitis

Case	Disease	Sex/age/ duration (y)	Previous IS	Clinical involvement at beginning of rituximab treatment	No of infusions × dose (mg)/No of MP pulses/ concomitant IS	Adverse event (Y/N)	Efficacy (Y/N)	Time to response (w)/ follow up (m)	Prednisone initial/last	Auto-Ab initial/last	HCV load (initial/M3/M12) (logIU/ml)	Relapse (Y/N)/ time to relapse (m)
34	Type II MC	F/53/2	IFN+ribav	Renal	3×375.m^{-2}/3/MP (1000)	Encephalopathy	N	–/9	20/7.5	Cryo: pos/pos RF: pos/pos	6.4/7.3/6.3	–
35	Type II MC	F/66/18	IFN+ribav/inflix	Skin, nerve, renal	4×375.m^{-2}	Infusion related	Y	4/20	20/5	Cryo: (mg/l) 1104/neg RF: 289/neg	5.7/6.5/5.1	Y/13
36	Rheumatoid vasculitis	F/38/11	HQ/MTX/CPH/ plasmaph/inflix	Nerve, myocardial, intestinal	3×375.m^{-2}/2/MP (500)/CPH	N	Death	–/1.5	60/60	NA	–	–
37	Wegener's syndrome	M/31/1	CPH/AZA inflix/ MTX	ENT, lung	3×375.m^{-2}/3/MP (200) plasmaph	N	N	–/9	15/15	cANCA: pos/pos	–	–
38	Wegener's syndrome	M/60/13	CPH/ivlg/AZA/ MMF/inflix	ENT; pyoderma gangrenosum	15×375.m^{-2}/MTX+MMF	N	Y	4/24	5/5	Anti-PR3 (ELISA): 90 IU/neg	–	N

anti-PR3, anti-proteinase 3 antibody; auto-Ab, autoantibody; AZA, azathioprine; CPH, cyclophosphamide; cryo, cryoglobulinaemia; ELISA, enzyme linked immunosorbent assay; ENT, ear, nose, throat; F, female; HCV, hepatitis C virus; IFN, interferon; inflix, infliximab; IS, immunosuppressants; ivlg, intravenous immunoglobulin; m, months; M, male; MC, mixed cryoglobulinaemia; MMF, mycophenolate mofetil; MP, methylprednisolone; MTX, methotrexate; N, no; NA, not available; neg, negative; plasmaph, plasmapheresis; pos, positive; RF, rheumatoid factor (IU/ml, determined by nephelometry); ribav, ribavirin; w, weeks; y, years; Y, yes; –, not relevant.

Table 5 Demographic, clinical, and biological data on five patients treated with rituximab for diverse autoimmune diseases

Case	Disease	Sex/age/duration (y)	Previous IS	Clinical involvement at beginning of rituximab treatment	No of infusions × dose (mg)/No of MP pulses/concomitant IS	Adverse event (Y/N)	Efficacy (Y/N)	Time to response (w)/follow up (m)	Prednisone initial/last	Auto-Ab initial/last	Relapse (Y/N)/time to relapse (m)
39	Anti-synthetase syndrome	F/55/19	ALC/HQ/ivlg/MTX	Polymyositis/pemphigus	4×375.m^{-2}	N	Y	4/7	20/18	Anti-Jo1: pos/pos	Y/4
40	Anti-synthetase syndrome	F/53/6	MTX/AZA/ivlg	Polymyositis	4×375.m^{-2}	N	Y	4/5	20/10	Anti-Jo1: pos/pos	N
41	Sarcoidosis	M/37/17	No	Cervical and mesenteric lymphadenopathy	4×375.m^{-2}	N	Y	8/11	20/10	–	Y/5
42	Still's disease	F/32/15	MTX/inflix/HQ/CIC	Polysynovitis	2×375.m^{-2}/2/MP (1000)/CPH	N	N	–/2	100/100	–	–
43	Systemic sclerosis	M/57/6	CPH/SCT/fluda	Systemic sclerosis	5×375.m^{-2}/fluda	N	N	–/5	Neg/neg	Anti-SCL70: pos/pos	–

ALC, Allochrysine (sodium aurothiopropanol sulphonate); auto-Ab, autoantibody; AZA, azathioprine; CIC, ciclosporine; CPH, cyclophosphamide; F, female; fluda, fludarabin; HQ, hydroxychloroquine; inflix, infliximab; IS, immunosuppressants; ivlg, intravenous immunoglobulin; m, months; M, male; MP, methylprednisolone; MTX, methotrexate; N, no; NA, not available; neg, negative; pos, positive; SCT, autologous stem cell transplantation; w, weeks; y, years; Y, yes; –, not relevant.

back to work four months after rituximab treatment. Anti-Jo1 antibody remained detectable in both patients.

Rituximab alone had a dramatic clinical effect on cervical lymphadenopathy as well as a clear corticosteroid sparing effect in one patient with lymph node sarcoidosis (case 41), who achieved complete remission after treatment.

No efficacy of rituximab was observed in one patient treated with rituximab and cyclophosphamide for severe Still's disease and polysynovitis (case 42). Rituximab and fludarabin had no effect on the clinical course of systemic sclerosis in one patient who had previously experienced relapse after high dose cyclophosphamide and autologous stem cell transplantation (case 43).

Monitoring B cell depletion

B cell depletion (defined as a peripheral CD19+B lymphocyte count of less than 5 cells/μl), which was assessed in only 12 patients, was observed in all but one, in whom rituximab treatment was unsuccessful (case 29). Two of the 11 remaining patients, whose B cell pool was depleted, did not respond to rituximab (cases 13 and 17).

Monitoring of HCV load

Three patients had antibodies against hepatitis C, including two with cryoglobulinaemia related vasculitis (cases 34 and 35) and one with SLE (case 22). HCV load was not detectable in patient 22 before treatment and remained undetectable after rituximab. In the two patients with cryoglobulinaemia, HCV viral load increased shortly after rituximab and then returned to baseline (table 4).

DISCUSSION

This retrospective study shows that despite the absence of marketing authorisation, rituximab is used in various refractory autoimmune diseases in daily rheumatological practice. The use of rituximab for off-label autoimmune diseases might even be more common, as this retrospective study depended on the recall of clinicians to identify cases. Short term efficacy could be observed in 70% of the patients. Additionally, rituximab treatment allowed a reduction in oral corticosteroids by 9.5 mg/day, on average, in responders. Limitations to this retrospective study include the heterogeneity of the diseases studied and the rather short follow up duration, which prevents us from drawing definite conclusions about the long term efficacy of rituximab. This led us to concentrate mainly on the tolerance of rituximab in these 43 patients with autoimmune diseases.

In practice, tolerance was good and in accordance with the published data. Two patients (cases 10 and 35) with infusion related reactions experienced the same side effects with infliximab, another chimeric monoclonal antibody. In these patients, a cross allergy to the mouse component could be hypothesised. The two patients who experienced the most severe side effects (encephalopathy and sepsis-like syndrome) had renal functional impairment. Serum sickness-like reactions, which occurred repeatedly in three patients, have been described in patients treated with rituximab.[5–7] The three deaths appeared to be a consequence of the refractory character of the autoimmune disease and not of intolerance to rituximab.

The main experience of rituximab in autoimmune diseases comes from a controlled trial in rheumatoid arthritis.[4] In that study, 43% (rituximab and methotrexate) and 41% (rituximab and cyclophosphamide) of patients with RA achieved 50% improvement according to the ACR criteria, compared with 13% of patients given methotrexate alone. Our results compare well with that of the controlled trial, showing comparable efficacy and tolerance of rituximab in patients

not under trial conditions, including nine in whom anti-TNF therapy had failed.

The first published open study[8] of SLE included six patients with severe SLE treated with rituximab, high dose steroids, and cyclophosphamide, which led to clinical improvement in five patients. The same group reported the results of six patients with nephritis: four of them experienced a marked improvement in lupus activity and in serological and renal features.[9] Recently, another group reported the efficacy of rituximab added to current therapy in 18 patients.[10] Clinical activity of lupus markedly decreased in 10 patients in whom B cells were depleted. No overall change in serum levels of anti-dsDNA antibodies was observed. There are a few case reports of treatment with rituximab for autoimmune haemolytic anaemia,[11] thrombocytopenia,[12] and neurological involvement with secondary antiphospholipid syndrome[13] in patients with SLE.

In the present study, two of the four SLE patients with active nephritis and seven of the nine without nephritis responded to rituximab. These results suggest the potential use of rituximab in severe SLE, as two of four patients with lupus nephritis and one with central nervous system involvement were greatly improved. Additionally, rituximab had a marked corticosteroid sparing effect in milder but corticosteroid dependent forms of lupus with cutaneous or articular involvement, as it allowed the daily prednisone dosage to be decreased in responders by more than threefold on average. No conclusions on the effect of rituximab on anti-dsDNA levels can be drawn, given the limited number of patients assessed.

In pSS, the first published observation described self reported subjective improvement in oral and ocular dryness following treatment with rituximab for parotid marginal zone lymphoma.[14] Recently, the clinical evolution of four patients treated with rituximab for pSS associated lymphoma was reported.[15] Type II mixed cryoglobulinaemia (MC), observed in three patients, disappeared. No information was given about the evolution of sicca syndrome. In the present study, extraglandular symptoms—notably swelling of the parotid gland, arthralgias, and cryoglobulinaemia related vasculitis—were sensitive to rituximab in all but one patient. A decrease in the level of RF or cryoglobulinaemia, or both, accompanied the clinical improvement in extraglandular signs in the responders. However, no conclusions can be drawn about effect of rituximab on dryness.

For patients with vasculitis and HCV related type II MC, the greatest experience comes from two Italian studies involving 15 and 20 patients each.[16 17] A significant increase in the level of HCV RNA was observed in responders in one of the series, as in two of our patients (including one responder). Thus the association of antiviral treatment with rituximab could be considered in patients with replicating hepatitis C. The present study involved four patients with cryoglobulinaemia (two HCV related, two pSS related). Rituximab had a major effect on purpura and skin ulcers in three patients and on peripheral nerve involvement in two. Cryoglobulinaemia disappeared in the three responders. In relation to ANCA related vasculitis, only one case of Wegener's granulomatosis, with good response to rituximab in combination with cyclophosphamide and high dose steroids, was reported.[18] The present study involved two patients with Wegener's granulomatosis, in whom treatment with cyclophosphamide had been unsuccessful. Only one patient responded well to rituximab, with a concomitant marked improvement in pyoderma gangrenosum and the disappearance of antiproteinase 3 antibody.

Clinicians involved in the study also used rituximab for other inflammatory arthritides such as antisynthetase syndrome, sarcoidosis, systemic sclerosis, and Still's disease, for which no case reports have been published. Rituximab could be a promising therapeutic strategy in antisynthetase syndrome, as it normalised muscular strength and muscle enzyme levels and reduced corticosteroid dosage in our two patients. Likewise, rituximab has shown good efficacy in five patients with refractory dermatomyositis.[19] The efficacy of rituximab in sarcoidosis, observed in one patient, also requires further study.

Interestingly, almost half the responders received rituximab concomitantly with immunosuppressants. Among the seven patients who experienced clinical relapse of the disease, five had taken rituximab alone. Thus in autoimmune diseases, combination therapy might improve the efficacy of rituximab, as shown in rheumatoid arthritis,[4] and might delay the occurrence of relapses.

A decrease in B cell count paralleled clinical efficacy in nine patients and the count was stable in one patient in whom treatment with rituximab was unsuccessful. In patients who experience relapse, clinical manifestations of disease are often preceded by the reappearance of B cells or autoantibodies or both,[20] which could be observed in three patients (reappearance of B cells in one patient with SLE, of anti-dsDNA antibodies in another patient with SLE, and of cryoglobulinaemia in one patient with HCV related vasculitis).

This study showed good tolerance, short term clinical efficacy, and marked reduction in corticosteroid use with rituximab treatment in patients with various refractory autoimmune diseases. Controlled trials should be carried out to explore the therapeutic effect of rituximab in SLE, pSS, vasculitis, and polymyositis.

ACKNOWLEDGEMENTS

We thank Olivier Meyer and Christophe Richez for their collaboration. We are indebted to Stephanie Poulain, Arielle Rosenberg, and Matthieu Tamby for HCV viral load assessment.

Authors' affiliations

J-E Gottenberg, X Mariette, Service de Rhumatologie, Hôpital de Bicêtre, Le Kremlin-Bicêtre, France
O Lambotte, Service de Médecine Interne, Hôpital de Bicêtre
L Guillevin, Service de Médecine Interne, Hôpital Cochin, Paris
B Combe, Service d'Immuno-Rhumatologie, Hôpital Lapeyronie, Montpellier, France
Y Allanore, Service de Rhumatologie A, Hôpital Cochin, Paris
A Cantagrel, Service de Rhumatologie, Centre Hospitalier Universitaire (CHU), Rangueil, Toulouse, France
C Larroche, Service de Médecine Interne, Hôpital Avicenne, Bobigny, France
M Soubrier, Service de Rhumatologie, CHU Gabriel Montpied, Clermont-Ferrand, France
L Bouillet, Service de Médecine Interne, CHU de Grenoble, Grenoble, France
M Dougados, Service de Rhumatologie B, Hôpital Cochin, Paris
O Fain, Service de Médecine Interne, Hôpital Jean Verdier, Bondy, France
D Farge, Service de Médecine Interne, Hôpital Saint-Louis, Paris
X Kyndt, Service de Nephrologie et Médecine Interne, CHU de Valenciennes, Valenciennes, France
O Lortholary, Service de Maladies Infectieuses et Tropicales, Hôpital Necker-Enfants Malades, Paris
C Masson, Service de Rhumatologie, CHU d'Angers, Angers, France
B Moura, Service de Rhumatologie, Hôpital Ambroise Paré, Boulogne, France
P Remy, Service de Nephrologie, Hôpital Henri Mondor, Créteil, France
T Thomas, Service de Rhumatologie, CHU Saint-Etienne, Saint-Etienne, France
D Wendling, Service de Rhumatologie, CHU Jean Minjoz, Besançon, France
J-M Anaya, Unidad de Reumatología CIB, Universidad Pontificia Bolivariana, Medellin, Colombia
J Sibilia, Service de Rhumatologie, Hôpital Hautepierre, Strasbourg, France

REFERENCES

1 **Mamula MJ**, Fatenejad S, Craft J. B cells process and present lupus autoantigens that initiate autoimmune T cell responses. *J Immunol* 1994;**152**:1453–61.
2 **Harris DP**, Haynes L, Sayles PC, Duso DK, Eaton SM, Lepak NM, *et al*. Reciprocal regulation of polarized cytokine production by effector B and T cells. *Nat Immunol* 2000;**1**:475–82.
3 **Moulin V**, Andris F, Thielemans K, Maliszewski C, Urbain J, Moser M. B lymphocytes regulate dendritic cell (DC) function in vivo: increased interleukin 12 production by DCs from B cell-deficient mice results in T helper cell type 1 deviation. *J Exp Med* 2000;**192**:475–82.
4 **Edwards JC**, Szczepanski L, Szechinski J, Filipowicz-Sosnowska A, Emery P, Close DR, *et al*. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. *N Engl J Med* 2004;**350**:2572–81.
5 **D'Arcy CA**, Mannik M. Serum sickness secondary to treatment with the murine-human chimeric antibody IDEC-C2B8 (rituximab). *Arthritis Rheum* 2001;**44**:1717–18.
6 **Herishanu Y**. Rituximab-induced serum sickness. *Am J Hematol* 2002;**70**:329.
7 **Hellerstedt B**, Ahmed A. Delayed-type hypersensitivity reaction or serum sickness after rituximab treatment. *Ann Oncol* 2003;**14**:1792.
8 **Leandro MJ**, Edwards JC, Cambridge G, Ehrenstein MR, Isenberg DA. An open study of B lymphocyte depletion in systemic lupus erythematosus. *Arthritis Rheum* 2002;**46**:2673–7.
9 **Leandro MJ**, Edwards JC, Manson J, Cambride G, Isenberg DA. Treatment of refractory lupus nephritis with B lymphocyte depletion. *Arthritis Rheum* 2003;**48**:S378:924.
10 **Looney RJ**, Anolik JH, Campbell D, Felgar RE, Young F, Arend LJ, *et al*. B cell depletion as a novel treatment for systemic lupus erythematosus. A phase I/II dose-escalation trial of rituximab. *Arthritis Rheum* 2004;**50**:2580–9.
11 **Perrotta S**, Locatelli F, La Manna A, Cennamo L, De Stefano P, Nobili B. Anti-CD20 monoclonal antibody (Rituximab) for life-threatening autoimmune haemolytic anaemia in a patient with systemic lupus erythematosus. *Br J Haematol* 2002;**116**:465–7.
12 **ten Cate R**, Smiers FJ, Bredius RG, Lankester AC, van Suijlekom-Smit LW, Huizinga TW, *et al*. Anti-CD20 monoclonal antibody (rituximab) for refractory autoimmune thrombocytopenia in a girl with systemic lupus erythematosus. *Rheumatology* 2004;**43**:244.
13 **Weide R**, Heymanns J, Pandorf A, Koppler H. Successful long-term treatment of systemic lupus erythematosus with rituximab maintenance therapy. *Lupus* 2003;**12**:779–82.
14 **Somer BG**, Tsai DE, Downs L, Weinstein B, Schuster SJ. Improvement in Sjogren's syndrome following therapy with rituximab for marginal zone lymphoma. *Arthritis Rheum* 2003;**49**:394–8.
15 **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* 2004;**43**:1050–3.
16 **Sansonno D**, De Re V, Lauletta G, Tucci FA, Boiocchi M, Dammacco F. Monoclonal antibody treatment of mixed cryoglobulinemia resistant to interferon alpha with an anti-CD20. *Blood* 2003;**101**:3818–26.
17 **Zaja F**, De Vita S, Russo D, Michelutti A, Fanin R, Ferraccioli G, *et al*. Rituximab for the treatment of type II mixed cryoglobulinemia. *Arthritis Rheum* 2002;**46**:2252–4.
18 **Specks U**, Fervenza FC, McDonald TJ, Hogan MC. Response of Wegener's granulomatosis to anti-CD20 chimeric monoclonal antibody therapy. *Arthritis Rheum* 2001;**44**:2836–40.
19 **Levine TD**. Rituximab in the treatment of dermatomyositis: an open-label pilot study. *Arthritis Rheum* 2005;**62**:601–7.
20 **Cambridge G**, Leandro MJ, Edwards JC, Ehrenstein MR, Salden M, Bodman-Smith M, *et al*. Serologic changes following B lymphocyte depletion therapy for rheumatoid arthritis. *Arthritis Rheum* 2003;**48**:2146–54.

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

J-E Gottenberg, L Guillevin, O Lambotte, B Combe, Y Allanore, A Cantagrel, C Larroche, M Soubrier, L Bouillet, M Dougados, O Fain, D Farge, X Kyndt, O Lortholary, C Masson, B Moura, P Remy, T Thomas, D Wendling, J-M Anaya, J Sibilia and X Mariette

Ann Rheum Dis 2005 64: 913-920 originally published online November 18, 2004
doi: 10.1136/ard.2004.029694