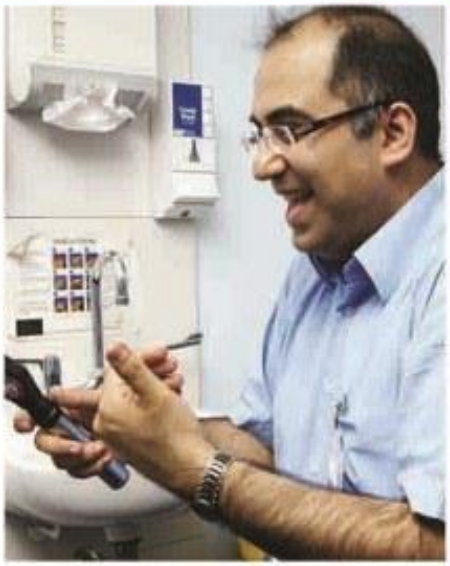
NHS England

Interim Clinical Commissioning Policy Statement: Rituximab for the treatment of Systemic Lupus Erythematosus in adults

August 2013

Reference: NHS ENGLAND A13/PS/a



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NHS England

Clinical Commissioning Policy Statement: Rituximab for the treatment of Systemic Lupus Erythematosus in adults

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POLICY STATEMENT: Rituximab for the treatment of Systemic Lupus Erythematosus in adults	**Policy Ref:** **NHS England** **A13/PS/a**

Background:	There are approximately 15,000 people in England and Wales with SLE, predominately women, with a peak incidence at the age of 25-30 years old. The incidence and prevalence of SLE is higher in African-Caribbean, South Asian and Chinese populations compared to European whites (1;2). In these racial/ethnic groups thedisease also tends to be more severe and in particular there is a higher incidence of renal involvement (3). SLE can affect any organ system, sequentially or at the same time. Effective management involves accurately assessing both disease activity and damage (i.e. permanent change) in all organ systems. There are several validated scoring systems for this purpose (BILAG 2004, SLEDAI-2K, SLICC), which are in use in specialised centres and in clinical trials (4-6). Renal involvement (glomerulonephritis) occurs in up to 40% of cases, has a key role in prognosis, and is associated with a higher mortality rate. It can occur many years after diagnosis, although is usually apparent within 5 years. Approximately 10% of patients with lupus nephritis develop end-stage renal failure requiring dialysis or transplantation. The aim of drug therapy is to treat disease activity and prevent disease flares. Therapy is dictated by both organ involvement and severity of individual manifestations. Antimalarials (especially hydroxychloroquine), azathioprine and methotrexate, in combination with corticosteroids are commonly prescribed. These regimes are effective for the majority of patients who have mild-moderate skin and joint disease. Approximately 20-30% of patients continue to have high disease activity despite these standard therapies or have organ involvement particularly associated with a worse prognosis e.g. renal, neuropsychiatric, haematological involvement. This group will require therapy with more potent immunosuppression such as intravenous cyclophosphamide or mycophenolate mofetil. A proportion of these patients will however continue to have active uncontrolled disease despite these agents, or will have unacceptable toxicities from such drugs. In others, disease control will require an unacceptably high dose of corticosteroids which, in

	this population, is associated with the development of significant co-morbidities such as bone, cardiovascular and metabolic consequences (7;8). These patients will require access to both specialised clinical advice and access to treatment with a biologic drug such as rituximab. Rituximab is currently used in specialised centres in England in this clinical setting, and there is an existing national registry, the BILAG Biologics Register (www.bilagbr.org). Currently, less than 10% of all cases of SLE have disease of a severity requiring such an approach. The aim of this policy statement is to make access to the drug equitable across the country for the specific groups of patients indicated. Section amended from original- please see change notice at foot of document
Commissioning position:	Rituximab will only be funded for use in Systemic Lupus Erythematosus (SLE) where the following criteria are met: 1. Diagnosis of SLE (fulfilling either ACR or SLICC criteria) AND 2. Active disease (defined as at least one BILAG A score and/or 2B scores, or a SLEDAI-2K score >6) AND 3. Failure to respond or having adverse events to, two or more standard immunosuppressive therapies (one of which must be either mycophenolate mofetil or cyclophosphamide, unless contraindicated) in combination with corticosteroids. A failed response is defined as being unable to achieve sustained disease control and still having evidence of at least one BILAG A or at least 2 BILAG B scores (or requiring unacceptably high levels of long term oral corticosteroids to maintain a lower disease activity state). 4. All patients who meet the above criteria of refractory disease activity sufficient to justify the use of rituximab, must be managed at, or in collaboration, with a centre commissioned to provide specialised services that has expertise in the assessment and management of SLE. 5. All patients receiving rituximab for SLE must be registered with the BILAG Biologics Register (www.bilagbr.org). All SLE patients with refractory disease activity should also be given the opportunity to be considered for clinical trials assessing therapies for the treatment of active SLE. **Response Definition:** Response to therapy should be assessed by 6 months for non-renal disease and at 6 and 12 months for patients with lupus

	nephritis. These definitions of response are based on validated outcome measures utilised in the most recent SLE clinical trials. For **non-renal disease** a clinically meaningful response by 6 months will be defined as: -BILAG A scores reduced to a B score or less AND BILAG B scores reduced to C or D. -AND/OR SLEDAI-2K reduced by 4 or more points from baseline. For **renal disease**: a response will be assessed at 6 and 12 months, and by 12 months a response will be defined as: - >50% improvement in proteinuria and normalisation or stabilisation of eGFR from baseline values. Any response should also occur in the context of either a stable or reduced steroid dose requirement compared to baseline, especially in the 8 weeks prior to the 6-month clinical assessment. **<u>Dosing Regimes:</u>** In England, the main protocol in use is: IV rituximab 1000 mg on day 1 and 15 of an infusion cycle (with or without low dose cyclophosphamide). After which patients are retreated if they have been deemed a responder and when they are developing a further flare of disease (9). For re-treatment of such patients, re-treatment is permitted if the clinician assessment is that a flare is now beginning, even if the BILAG score criteria for initial therapy is not yet achieved (e.g. recurrence of one or more B scores without waiting for an A score). This is necessary because severe flares carry a risk of further organ damage for the patient.
Effective from:	August 2013
Evidence summary:	The beneficial effects of Rituximab in active SLE, refractory to standard immunosuppression, have been reported in 24 case series from specialised lupus centres throughout the world, including England. There is a consistency of reported improvement across all case series, despite use of different end points. Use of Rituximab in this setting is also recommended within Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association recommendations for the management of adult and paediatric lupus nephritis published November 2012 (16). There have been two RCTs of Rituximab in SLE, the LUNAR (Lupus Nephritis Assessment with Rituximab) and EXPLORER (Exploratory Phase 2/3 SLE Evaluation of Rituximab) studies, which enrolled 144 and 257 patients with non-renal and renal disease respectively (10;11). Although neither study achieved their

	primary end-point, it is recognised that there were important design limitations in these trials, including issues with end-point measurements, the very high use of concomitant steroids in combination with other immunosuppressives in both treatment arms, as well as being underpowered to detect a clinically meaningful improvement (12,17,18). More importantly, there are also significant differences between the subjects that were enrolled in these two studies, and the patient cohort proposed in this commissioning policy, namely, patients with refractory disease in whom standard of care treatment has failed. The clinical trials added rituximab on top of standard therapy for non-refractory patients, and also those patients who had failed standard therapies (cyclophosphamide) were excluded from the trials, as were patients with severe organ-threatening manifestations(12). Usual practice in England is to withdraw background immunosuppression when initiating rituximab (9). Despite these limitations, pre-specified secondary analyses did suggest efficacy of rituximab in several patient subsets, including significantly fewer ($p< 0.01$) patients in the rituximab group requiring cyclophophosphamide for worsening disease. There were also serological improvements, with significant effects on anti-dsDNA antibodies and complement levels. Both these tests are sensitive bloodstream markers of lupus-specific disease activity This is an important observation, because improvement in these parameters is known to be a predictor of clinical response, and also support biological efficacy of rituximab. Recent open-label studies strongly support the clinical efficacy of rituximab particularly in the group of refractory SLE populations to whom this commissioning policy will apply. Lu et al studied 50 patients, and of 45 patients with adequate follow-up, 19(42%) achieved remission at the 6 month time point (9). Li et al studied patients with lupus nephritis treated with rituximab with or without cyclophosphamide (13) . Of the 19 patients recruited 4 (21%) had a complete response at 48 weeks using the SLICC Renal Response Criteria. 11 (58%) had a partial response and 4 patients (22%) were stable or worsened at 48 weeks. A case series of 164 patients with biopsy proven lupus nephritis from England and Spain, the majority of whom had refractory or relapsing disease, reported a complete or partial response (>50% improvement in all renal parameters) in 67% of patients at 6 months after rituximab (14). A recent systematic analysis of studies in refractory lupus nephritis (300 patients) reported a complete or partial response in 67- 87% of patients, according to lupus nephritis subtype (20). Similarly, a meta-analysis of 188 patients from open-label studies noted an overall 91% response rate within the cases reported and

	even an 89.3% response in patients with CNS involvement (15). Efficacy has also been reported amongst 136 patients in the French Autoimmunity and Rituximab registry of patients with both renal and non-renal disease, with improvements in articular, cutaneous, renal and haematological manifestations (19). Although there are important limitations of open-labelled studies, the overall experience of the use of rituximab in refractory lupus is that there is a definite efficacy of this agent in patients that have failed conventional combination therapy (corticosteroids, hydroxychloroquine and immunosupressants). Whilst the magnitude of improvement in individual patients is variable, there is clear evidence that rituximab offers an important therapeutic option for people living with severe SLE that has been refractory to existing conventional therapies.
Equality impact:	Throughout the production of this document, due regard has been given to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited in under the Equality Act 2010) and those who do not share it
Responsible CRG:	Rheumatology CRG
Mechanism for Funding:	Funding is transacted as per local contract agreements and terms.
Date Approved by Clinical Priorities Advisory Group	12 July 2013
Policy review date:	During 2014

References

(1) Samanta A, Roy S, Feehally J, Symmons DP. The prevalence of diagnosed systemic lupus erythematosus in whites and Indian Asian immigrants in Leicester city, UK. Br J Rheumatol 1992 Oct;31(10):679-82.

(2) Johnson AE, Gordon C, Palmer RG, Bacon PA. The prevalence and incidence of systemic lupus erythematosus in Birmingham, England. Relationship to ethnicity and country of birth. Arthritis Rheum 1995 Apr;38(4):551-8.

(3) Patel M, Clarke AM, Bruce IN, Symmons DP. The prevalence and incidence of biopsy-proven lupus nephritis in the UK: Evidence of an ethnic gradient. Arthritis Rheum 2006 Sep;54(9):2963-9.

(4) Yee CS, Isenberg D, Farewell V, Akil M, Bowman S, Bruce I, et al. BILAG-2004 index: A reliable tool for assessment of SLE activity. Arthritis Rheum 2005 Sep;52(9):S189.

(5) Gladman DD, Ibanez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. J Rheumatol 2002 Feb;29(2):288-91.

(6) Gladman DD, Goldsmith CH, Urowitz MB, Bacon P, Fortin P, Ginzler E, et al. The Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index for Systemic Lupus Erythematosus International Comparison. J Rheumatol 2000 Feb;27(2):373-6.

(7) Gladman DD, Urowitz MB, Rahman P, Ibanez D, Tam LS. Accrual of organ damage over time in patients with systemic lupus erythematosus. J Rheumatol 2003 Sep;30(9):1955-9.

(8) Parker B, Urowitz MB, Gladman DD, Lunt M, Bae SC, Sanchez-Guerrero J, et al. Clinical associations of the metabolic syndrome in systemic lupus erythematosus: data from an international inception cohort. Ann Rheum Dis 2012 Sep 22.

(9) Lu TY, Ng KP, Cambridge G, Leandro MJ, Edwards JC, Ehrenstein M, et al. 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.

(10) Merrill JT, Neuwelt CM, Wallace DJ, Shanahan JC, Latinis KM, Oates JC, et al. Efficacy and Safety of Rituximab in Patients with Moderately to Severely Active Systemic Lupus Erythematosus (SLE): Results from the Randomized, Double-blind Phase II/III Study EXPLORER. Arthritis Rheum 2008 Dec;58(12):4029-30.

(11) Rovin BH, Furie R, Latinis K, Looney RJ, Fervenza FC, Sanchez-Guerrero J, et al. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. Arthritis Rheum 2012 Apr;64(4):1215-26.

(12) Bruce IN. Re-evaluation of biologic therapies in systemic lupus erythematosus. Curr Opin Rheumatol 2010 May;22(3):273-7.

(13) Li EK, Tam LS, Zhu TY, Li M, Kwok CL, Li TK, et al. Is combination rituximab with cyclophosphamide better than rituximab alone in the treatment of lupus nephritis? Rheumatology (Oxford) 2009 Aug;48(8):892-8.

(14) az-Lagares C, Croca S, Sangle S, Vital EM, Catapano F, Martinez-Berriotxoa A, et al. Efficacy of rituximab in 164 patients with biopsy-proven lupus nephritis: pooled data from European cohorts. Autoimmun Rev 2012 Mar;11(5):357-64.

(15) Ramos-Casals M, Garcia-Hernandez FJ, de RE, Callejas JL, Martinez-Berriotxoa A, Pallares L, et al. Off-label use of rituximab in 196 patients with severe, refractory systemic autoimmune diseases. Clin Exp Rheumatol 2010 Jul;28(4):468-76.

(16). Bertsias GK, Tektonidou M, Amoura Z, et al. Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. Ann Rheum Dis 2012;71:1771-1782.

(17). Harvey P, Gordon C B-Cell Targeted Therapies in Systemic Lupus Erythematosus. Successes and Challenges. BioDrugs (2013) 27:85–95

(18). Ding H, Gordon C New biologic therapy for systemic lupus erythematosus Current Opinion in Pharmacology 2013, 13:405–412

(19) Terrier B, Amoura Z et al. Safety and efficacy of rituximab in systemic lupus erythematosus: results from 136 patients from the French AutoImmunity and Rituximab registry. Arthritis Rheum 2010, 62:2458-2466.

(20) Weidenbusch M, Rommele C, Schrottle A, Anders HJ: Beyond the LUNAR trial. Efficacy of rituximab in refractory lupus nephritis. Nephrol Dial Transplant 2013, 28:106-111.

Version Control Sheet

Version	Section/Para/Appendix	Version/Description of Amendments	Date	Author/Amended by
1	Version 1		12/7/2013	Rheumatology CRG
2				
3				
4				
5				
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7				
8				
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Change Notice for Published Specifications and Products

developed by Clinical Reference Groups (CRG)

Amendment **to the Published Products**

Product Name	Interim Clinical Commissioning Policy Statement: Rituximab
Ref No	**A13/PS/a**
CRG Lead	Sarah Watson

Description of changes required

Describe what was stated in original document	Describe new text in the document	Section/Paragraph to which changes apply	Describe why document change required	Changes made by	Date change made
transplant centres throughout England either through prior approval or IFRs.	Text deleted	Background section Page 5	Part of sentence included in error	Sarah Watson	September 2013
Prepared by the NHS England Clinical Reference Group for Rheumatology	Prepared by the NHS England Clinical Reference Group for Specialised Rheumatology	Page 2	Insertion of the word 'Specialised' into title	Sarah Watson	September 2013