SPECIALISED COMMISSIONING – RESPONSE TO AMENDMENTS REQUESTED TO EVIDENCE REVIEW DURING ENGAGEMENT OR CONSULTATION

URN	1853
POLICY TITLE	Rituximab for severe, refractory SLE (all ages)- draft policy proposition
CRG:	Specialised Rheumatology
NPOC:	Internal Medicine
Date:	14/03/2019

Description of comments during consultation	Two recent systematic reviews have been identified on the efficacy and safety of use of Rituximab in paediatric SLE as original policy proposition covered all ages. However the original ER did not include any evidence in children.
Action taken by Public Health lead	**Background to Paediatric SLE** Paediatric SLE (pSLE) is associated with more severe and active disease compared with systemic lupus erythematosus (SLE) in adults with a high incidence of renal and CNS involvement and worse health related outcomes including morbidity and mortality. The mechanism of action of Rituximab in children with SLE would be the same as in adults e.g. binding specifically to the CD20 antigen and mediating B-cell depletion, thereby preventing the renewal of autoantibodies and antigen presentation by pathogenic B cells. In JSLE, the inflammatory response is driven by autoantibodies and pro-inflammatory cytokines such as: IL-6, TNFa, IL-1B and type 1 IFNs. Current standard of care of JSLE involves the use of glucocorticoids, anti-malarials and

	immunosuppressant (ISS) drugs. However, some patients may have refractory disease or multiple, simultaneous manifestations requiring additional treatment(s) to control disease activity. Existing treatment regimens are associated with numerous debilitating side effects, with younger patients at increased risk due to the duration of their disease. Systemic corticosteroids have causal associations with Cushingoid features, hyperglycaemia, hyperlipidaemia, premature atherosclerosis, secondary osteoporosis and growth delay. Cytotoxic ISS drugs including cyclophosphamide (CYC), mycophenolate motefil (MMF), azathioprine (AZA) and methotrexate (MTX), increase the risk of teratogenicity, infection, infertility and cancer. Biological agents may potentially improve JSLE disease activity by targeting specific components of the pathological cascade, including B lymphocytes and B stimulatory molecules, T lymphocytes and co-stimulatory molecules, interferons and cytokines, 15 thereby preventing B and T cell activation, differentiation and survival. Biologics are being increasingly used in the routine care of JSLE patients, especially those with refractory disease or severe organ-specific manifestations. However, none of these agents has been approved for use in paediatric patients. <u>Summaries of the two Systematic Reviews in Paediatric SLE</u> **<u>First Systematic Review:</u>** Study: Peternecht E et al. The effectiveness and safety of biological therapeutics in juvenile onset systemic lupus erythematosus(JSLE): a systematic review Lupus (2018) 27, 2135–2145. Aim: The systematic review's aim was to systematically review and summarize the available literature regarding the effectiveness and safety of biologics in the treatment of JSLE. The period covered Jan 1st 2012 - Dec 7th 2016.

	The inclusion criteria for studies were: (i) Patients diagnosed with JSLE (age ≤18 years at diagnosis) (ii) Treatment with any biological agent (iii) Outcome measures assessing efficacy/effectiveness and safety were available Results: Forty- six studies were identified and nine selected as meeting the inclusion criteria. These included six cohort studies (1 prospective,5 retrospective), two case series and one pilot study covering a total study sample of 230 cases. In eight of these studies patients received Rituximab. The most common indication for initiation of biologics was active disease refractory to corticosteroids and/or immunosuppressant drugs with five studies including ≥ 50% patients with lupus nephritis (LN). The dose of RTX varied between 750mg/sq m on two occasions, a fortnight apart to 375- 500 mg/sq m weekly x 4 wks/a fortnight apart. Follow-up in the retrospective cohort studies and case series ranged from 0.1–13 years, and in the prospective cohort study and pilot study follow-up was 0.5 years and five years, respectively. Global Disease Activity: All but three studies used different disease activity scores/indices. Three of them used SLEDAI (SLE Disease Activity Index). All studies reported a short term (3-9 months) and long-term (12 months) reduction in scores and an improvement in disease activity after RTX initiation. Statistical significance was assessed and achieved in two of these studies. Notably, the pilot study had a follow-up period of five years, during which the reduced SLEDAI score was sustained. Two studies reported a statistically significant complete response/clinical improvement rate of the order of 64- 96%. Corticosteroid sparing effect: Seven studies demonstrated a significant steroid sparing effect by the addition of RTX. The range of reduction seen was 22%-75%-100% achieved both in the short (2.5 months) and longer term 21.5 months). Hypocomplementemia: In seven studies where hypocomplementemia was identified, mean/median complement levels e.g. C3 increased significantly and in a sustained manner with RTX. Anti-dsDNA levels: In most studies where these were reported, levels decreased with RTX with statistical significance reported by some.

	Specific disease manifestations: AITP and AIHA (Autoimmune Thrombocytopenic Purpura/ Autoimmune Haemolytic Anaemia) - In both these, high response rates to RTX were seen with restoration of haemoglobin and platelet parameters. Five studies included patients with renal manifestations. Laboratory measures (serum albumin, serum creatinine, proteinuria, urinary protein:creatinine ratio) demonstrated improved renal function in almost all of these patients. In one study renal remission was achieved within 3.5 months. One cohort study assessed JSLE patients with neuropsychiatric involvement: 94% patients demonstrated clinical improvement after RTX initiation. Repeat cycles: of RTX were required in 8–50% patients; however, clinical and laboratory improvement was reported in almost all cases. In one cohort study, survival analysis reported that the probability of flare at up to eight years after complete haematological response is reduced by < 40%. Safety: Severe (i.e. anaphylactic) infusion-related reactions were reported in three cohort studies at a with a median frequency of 4%. Two (2%) to 25% patients required hospitalization and/or intravenous antibiotics due to subsequent infection. Hypogammaglobulinaemia occurred transiently (not persistent in most cases) in the majority of patients and required treatment with IVIG. Overall, infusion reactions and infection were the most common adverse events, and in most instances, these were mild. However, there were several patients who required hospitalization for anaphylactic reactions, IV antibiotics or IVIG therapy. Summing up: This review has found that in JSLE patients, there was a significant improvement in disease activity, serum and urine markers of disease activity and reduced oral corticosteroid dose after RTX treatment. Conversely, up to 30% of patients required more than one course, several patients required treatment for severe infection and up to 13% developed hypogammaglobulinameia. Therefore it is important to monitor IgG levels before RTX therapy and RTX should be used cautiously in patients with pre-existing hypogammaglobulinaemia. It has also highlighted the paucity of high-quality interventional drug trials

	investigating biologics in juvenile systemic lupus erythematosus. Randomized controlled trials are needed to better evaluate the effectiveness and safety of bio logics in juvenile systemic lupus erythematosus. **Second Systematic Review:** Study: Mahmoud I et al. Efficacy and Safety of Rituximab in the Management of Paediatric Systemic Lupus Erythematosus: A systematic Review. J Pediatr 2017;187:213-9. The second systematic review searched relevant databases till 2016 for both clinical trials and observational studies of paediatric patients (aged <18 years) with SLE treated with RTX Twelve studies met the inclusion criteria. Description of study population: British, American, and Canadian studies were predominant (a total of 162 patients; 60% of a total of 262 patients). The patients were mostly female (80%) and ranged in age from 6 to 28 years. The mean age at onset of SLE was reported in 6 studies and ranged from 7.8 to 12.5 years. The age range for initiation of RTX was 6-19 years, overall. The mean duration of disease was reported in 9 studies and ranged from 1.4 to 4.7 years. Regarding previous therapies, all of the patients had failed to respond to cyclophosphamide and mycophenolate mofetil, and most had failed to respond to at least 1 other immunosuppressive agent (i.e. azathioprine, intravenous immunoglobulin, methotrexate, cyclosporine, tacrolimus, or thalidomide). The duration of follow-up ranged from 1 month to 36 months. Results of RTX Responses Clinical Indication: Refractory lupus nephritis was the most common indication for RTX therapy (7 studies). Other disease manifestations, including cytopenia (5 studies), vasculitis (3 studies), arthritis (3 studies), serositis (2 studies), neuropsychiatric disease (4 studies), skin disorders (2 studies), pulmonary hypertension (2 studies), ophthalmic

	disorders (1 study), and general symptoms (1 study). Dosing: There was heterogeneity in reported RTX regimens. The most common regimen was RTX infusion at a dose of 375 mg/m2/week. The number of doses per course ranged from 2 to 4, and the number of courses ranged from 1 to 12. Four studies reported a RTX dose of 750 mg/m2 (maximum 1 g) given as 2 intravenous infusions separated by approximately 14 days. Global disease Activity: Three studies reported short-term (1-8 months), statistically significant improvements in disease activity with 50%-96% complete remission and 36%-56% partial remission rates. Long -term (≥12 months) outcomes were reported by one study with 52% complete remission and 43% partial remission rates. Six of the 12 studies assessed disease activity using the SLE Disease Activity Index and described statistically significant improvement at 1, 3, 6, and 12 months. Two studies evaluated disease activity through the British Isles Lupus Activity Group score with one reporting a significant difference between scores from baseline to 1, 3, 6, and 12 months. Relapses were reported by 3 studies. Overall, the relapse rate ranged from 9% to 30%, and the median time to relapse ranged from 2 to 22 months. Clinical Manifestations: Renal Involvement: A total of 89 patients (33%) had nephritis before receiving RTX therapy. Significant improvement in renal function and reduction in proteinuria were achieved within 2-12 months in 7 studies. Three studies reported complete renal remission in 31%, 50%, and 25% of their cases, respectively with partial renal remission noted in 50% of their cases. One study reported that one of their seven patients who showed significantly improved renal function discontinued dialysis. Another study reported discontinuation of renal replacement therapy in two patients and declining urine albumin/creatinine ratio in all patients. This improvement in urine albumin/creatinine ratio was maintained at 18 months and was observed after all treatment episodes. Increasing serum albumin levels was also reported in 5 studies. Neuropsychiatric: Two

	studies in which neuropsychiatric manifestations were evaluated reported significant clinical improvement. Haematological involvement: Thirty-two children within four studies received RTX for refractory autoimmune cytopenia (22 with thrombocytopenia and 10 with haemolytic anaemia) with complete remission. The latter studies reported high and sustained rates of haematological remission. Immunologic: Two thirds of studies reported significant and sustained increases in C3 and C4 complement levels and significant decreases in double stranded DNA titres. Corticosteroid Reduction: More than half of included studies reported a significant decrease in corticosteroid doses in the short to long term (1-12 months). Safety: The most frequent adverse events were infusion reactions (n=14) and viral infections (n=10). Twenty-two patients experienced a serious adverse event, including severe cytopenia (n = 11), central nervous vasculitis (n = 1), and life-threatening infusion reaction (n = 2). Six patients developed severe infections that could be associated with RTX, including 2 patients with opportunistic infection. One study reported persistent hypogammaglobulinemia in several patients and progressive interstitial lung disease in 1 patient. Summing Up This review has found that RTX has been shown to be safe and effective for treating the renal and hematologic manifestations of pSLE, especially in terms of disease activity, immunologic measures, and steroid-sparing effect. Relapse prevention is a major goal of treatment for SLE. Whist relapses were reported in many studies, the severity of relapses was milder, rates of relapses were fewer, and time to relapse was longer in the patients who received RTX therapy. One third of patients had nephritis before receiving RTX therapy. RTX therapy reduced proteinuria even before immune changes became evident. In the review, RTX appeared to be safe. Adverse events were noted in 21% of patients. The most frequent adverse events were infusion reactions and infections.

Outcome	Based on the evidence from the two systematic reviews and the information contained in the PWG letter to the Clinical Panel which includes advice on clinical governance criteria and safety arrangements, the policy proposition should be amended to include all ages.