National Essential Medicine List
Tertiary Medication Review Process
Component: Antineoplastic Agents

MEDICINE MOTIVATION:

1. Executive Summary

Date: 28 February 2019
Medicine (INN): Rituximab
Medicine (ATC): L01XC02
Indication (ICD10 code): Refractory lupus nephritis (M32.1+) (Rescue therapy)
Patient population: Patients with lupus nephritis refractory to conventional immunosuppression therapy (mycophenolate mofetil (MMF), cyclophosphamide, azathioprine, corticosteroids). Corticosteroids are not direct comparators with rituximab.
Prevalence of condition: The prevalence of SLE in South Africa was estimated at 12.2 /100 000 in 1990. Approximately 1% of all patient on dialysis in South Africa have lupus nephritis.[1]
Level of Care: Tertiary
Prescriber Level: Specialist - Nephrologist
Current standard of Care: None
Efficacy estimates: (preferably NNT): Complete response in 30 – 64% of patients[8~~4~~, 11~~7~~, 12~~8~~, 13~~9~~, 14~~10~~, 17~~13~~] (observational studies/registry data/case series).

2. Name of author(s)/motivator(s)
Tertiary Expert Review Committee

3. Author affiliation and conflict of interest details
No conflicts of interest relating to this review.

4. Introduction/ Background[2]

Systemic lupus erythematosus (SLE) is a heterogeneous, multisystem, autoimmune disease characterized by the presence of multiple autoantibodies and the deposition of immune complexes in various tissues. SLE tends to most often affect women of reproductive age with manifestations ranging from low grade inflammation to fatal multi-organ damage.B cells are thought to play an important role in SLE pathogenesis by producing autoantibodies and secreting cytokines that regulate the activity of other immune cells. Loss of B cell tolerance is thought to be a pivotal event in the pathogenesis of SLE, providing a strong rationale for the study of targeted treatments that modify the effects of B cells on immunity.

Lupus nephritis (LN) is the most frequent serious manifestation of the disease. It has a key role in prognosis and is associated with a higher mortality rate. The reported incidence of clinically important kidney disease in systemic lupus is approximately 40%. Approximately 10% of patients with lupus nephritis develop end-stage renal failure requiring dialysis or transplantation and left untreated is associated with a 5-year survival rate varying from 0 to 20%.

The prevalence of SLE in South Africa was estimated at 12.2/100 000 patients in 1990. Infection and renal disease are the important causes of death in patients with SLE. Nephritis has been shown to be an independent predictor of mortality in SA. [1]

Patients with refractory disease are most likely to progress to end stage renal failure with the requirement of dialysis and/or transplant. In the public sector, there are insufficient resources available to dialyze all who present with end-stage renal failure. The dialysis prevalence rate in SA is 133 per million population. The transplant rate in SA is low at 4.7 per million population compared to other lower middle income countries.[3]

The incidence of kidney involvement differs with ethnicity. According to the Kidney Disease Improving Global Outcomes (KDIGO)[4] guidelines, the distribution of LN based on ethnicity is as follows:

KDIGO data on incidence

Race	Incidence
Caucasians	**12-33%**
Black African American	**40-69%**
Hispanic	**36-61%**
Asian(Indian or Chinese)	**47-53%**

The introduction of corticosteroids and immunosuppressive therapies, namely cyclophosphamide (CYP) and mycophenolate mofetil (MMF), which is less gonadotoxic than CYP, have improved prognosis to the extent that 5- and 10-year survival rates are approximately 95% and 90%, respectively. However, the rate of end-stage renal disease (ESRD) has remained static at 10–20% despite the availability of these therapies.[5]

Patients who fail all primary immunosuppressant therapy will invariably develop ESRD with its associated cost and poor prognostic implications. These will most likely be young patients who will not be guaranteed access to renal transplant due to the resource constraints.[6] Therefore the judicious use of rituximab **in this patient group;** will be to reduce the progression to ESRD and to prevent the development of stage 5 renal failure as rescue therapy when conventional treatment has failed.

There is no consensus definition of refractory LN, however a patient may be considered refractory if conventional cyclophosphamide regimens have been tried without success, and non-cyclophosphamide regimens have been unsuccessful.[4]

The patient should be confirmed adherent to conventional immunosuppression and have a repeat renal biopsy to confirm refractory lupus. The table below demonstrates the clinical definitions of complete and partial renal responses to treatment of lupus nephritis is from KDIGO.[4]

Complete renal response (CRR)	Return of serum creatinine to previous baseline	Decline in urine protein to creatinine ratio to < 0.5 mg/mmol
Partial renal response (PRR)	+/- 25% improvement in serum creatinine	50% decrease in proteinuria or protein to creatinine ratio < 300mg/mmol if nephrotic range

5. Purpose/Objective

- **P** Patients with lupus nephritis resistant to all conventional immunosuppression which includes corticosteroids, azathioprine, mycophenolate mofetil, and cyclophosphamide.
- **I** Rituximab 500 mg IV on day 0 and 14, repeated at 6 months as monotherapy

- **C** None - this is for rescue therapy in patients who have already failed conventional immunosuppression including mycophenolate mofetil and cyclophosphamide. These therapies may be continued to treat other extrarenal manifestations of lupus even if end stage renal disease develops.
- **O** Induce remission of refractory lupus nephritis
  Prevent progression of lupus nephritis and reduce steroid dose
  Prevent ESRD requiring dialysis and transplantation

6. Methods:

a. Data sources*:* PubMed, Cochrane Library

b. Search strategy :

Pubmed:

Rituximab AND lupus nephritis

("rituximab"[MeSH Terms] OR "rituximab"[All Fields]) AND ("lupus nephritis"[MeSH Terms] OR ("lupus"[All Fields] AND "nephritis"[All Fields]) OR "lupus nephritis"[All Fields]) - 200 results

Cochrane Library:

"Rituximab" - 36 systematic reviews. None relevant to refractory lupus nephritis.

Identified studies:

- RCT: Lunar trial (Rovin et. al. , 2012[7])
  - Reasons for inclusion: The trial investigated the use of rituximab in proliferative lupus nephritis and did not specifically include or recruit patients with refractory lupus nephritis. Patients were randomized without having failed any conventional therapy. However, secondary end-points showed hypothesis generating findings of: a significant reduction in steroid dose in the rituximab group, and only patients not on rituximab required rescue therapy with cyclophosphamide.
- Systematic analysis: Beyond LUNAR (Weidenbusch et al 2013[8])
  - Reasons for inclusion: systematic analysis of existing evidence to determine if Rituximab induced remission of lupus nephritis in patients failing conventional immunosuppression. The review supported the use of Rituximab for the induction of remission as a rescue in refractory lupus nephritis when conventional therapy has failed. Clinical registry data of rituximab also supported its use in refractory lupus nephritis

c. Excluded studies:

Review articles

Studies not involving rituximab

Author, date	***Type of study***	***Reason for exclusion***
Merril JT et. al. 2010 Jan; 62(1):222-33.[9] (EXPLORER Trial)	RCT	Rituximab not used specifically for lupus nephritis.
Tunnicliffe DJ, et. al. 2018, CD002922[10]	Cochrane Systematic Review	The review did not specifically investigate the use of rituximab in refractory lupus nephritis.

d. Evidence synthesis (confidence intervals have been included if available, often unreported)

Author, date	*Type of study*	n	Population	Comparators	Primary outcome	Effect sizes	Comments
Rovin et. al. , 2012[73] LUNAR STUDY	RCT	144	Class III or IV lupus nephritis	Rituximab as add on therapy to conventional immunosuppression versus conventional immunosuppression	Partial and complete renal response	The overall (complete and partial) renal response rates were 45.8% (n=33) among the 72 patients receiving placebo and 56.9% (n=41) among the 72 patients receiving rituximab (*P* = 0.18)	The patients studied did not have refractory lupus nephritis. Rituximab had no significant effect when used as add-on therapy but secondary analysis revealed less use of steroid therapy in rituximab group (p = 0.05), 12.8 mg (6.3 to 19.3mg, n = 72) versus 10.9 mg (6.8 to 15 mg, n = 72).
Weidenbusch et al 2013[84] BEYOND THE LUNAR STUDY	Systematic analysis or reports documenting outcomes of rituximab in patients with refractory LN	300	Resistant lupus nephritis (a collation of the results of different studies)	Rituximab used predominantly as alternate therapy to conventional immunosuppression	Partial and complete renal response	Rituximab induced a complete (between 40-60%) and partial response (between 67-85%) of lupus nephritis in patients who had failed both conventional therapies	The LN community considers RTX as an alternative rather than as an add-on drug instead of a top-of-standard of care
Alshaiki et.al.[11]	Meta-analysis of studies reporting outcome data with treatment of rituximab in SLE and Lupus Nephritis	31 Studies. 16 studies were retrospective case series, 14 were prospective case series,	Patients with refractory SLE or refractory lupus nephritis	Rituximab for patients refractory to conventional immunosuppression	Global response (complete response and partial) response after rituximab therapy.	Global response 70% (95% CI, 55%-81%). Complete response in 51% (95% CI, 34 – 68%). Partial response in 27% (95% CI, 18-39%).	Prednisone dose was significantly reduced after treatment with rituximab (p<0.001). Proteinuria was significantly reduced (p<0.001)

		2 were RCTs.					
Tanaka et al[17~~12~~]	Open label multi-center Prospective	34	Refractory lupus nephritis	Rituximab for patients refractory to conventional immunosuppression	Complete renal response and partial renal response	Complete response in 35.3 % and partial response in 23.5% with Overall response rate of 58.8% 95% CI (32.9-81.6%)	Reduction in proteinuria and prednisone dose.
Thorrun et al[12]	Observational prospective	25	Refractory lupus nephritis	Rituximab for patients refractory to conventional immunosuppression , combination with cyclophosphamide	Complete renal response and partial renal response	Complete response in 64% and partial response in 24% with overall response rate of 88%	Reduction in proteinuria with histological improvement on re-biopsy
Terrier et al[13]	Prospective registry data from 82 centres	42 of 136 patients with lupus nephritis	32 out of 42 patients with LN were refractory to conventional immunosuppression	Rituximab used in 67% refractory to MMF and 62% refractory to CYC. 24 % did not receive either	Complete renal response and partial renal response	Complete response in 45% and partial response in 29% with overall response of 74% in evaluated patients	Reduction in proteinuria with stable renal function
Diaz Lagares et al[14]	Case series	164	50% had refractory lupus nephritis	Most patients used standard immunosuppressives	In the refractory cohort	124 patients evaluated at 1 year. Partial response in 40% and complete response in 30% of this cohort	Statistically significant Improvement in serum albumin, proteinuria , eGFR

e. **Evidence quality:** It is difficult to provide high quality evidence when medicines are used as rescue therapies. Although the 2 randomized controlled trials using rituximab in SLE and LN did not reach their pre-specified end points, neither study specifically set out to investigate patient's refractory to existing conventional immunosuppressive therapy. There is however; consistent evidence from a systematic review, meta-analysis, open label observational studies as well as registry data to support rituximab's efficacy for patients with LN who are refractory to conventional therapy. [15,16,17,18,19] The evidence is from diverse geographical locations and across variety of demographic populations

7. Alternative agents:

There is no evidence for any alternative agents inducing remission in patients with resistant lupus nephritis. The intention for the use of rituximab in this indication is as a salvage therapy to prevent/delay the requirement for dialysis for which in the South African state sector is severely limited, and costly (~ R200 000/patient/year)[3].

8. Dose:

The Beyond the Lunar trial indicated that rituximab dosing and treatment intervals in various studies have been heterogeneous, and to date, there have been no reports that provide clear evidence that one regimen is more effective than others for B-cell depletion and response rates in refractory LN.

See below various regimens:

Rituximab regimen
375 mg/m^2/dose at 0, 1, 2, 3 weeks
750 mg/m^2/dose at 0 and 2 weeks
500mg/dose at 0 and 2 weeks
1000 mg/dose at 0 and 2 weeks

It is recommended that the 500mg dose at 0 and 2 weeks be used.

9. Safety

The adverse events associated with rituximab in refractory lupus nephritis were sepsis and infusion related reactions.

10. Estimated Budget Impact

Estimated numbers of refractory lupus nephritis per year in the South African Public Sector (as per correspondence with individual nephrology units).

Western Cape	
Groote Schuur Hospital	5
Tygerberg Hospital	5
Gauteng	
Charlotte Maxeke Academic Hospital	4
Chris Hani Baragwanath Hospital	5
George Mukhari Hospital	5
Steve Biko Academic Hospital	5
KwaZulu- Natal	
Inkosi Albert Luthuli Hospital	3
Greys Hospital	2
Eastern Cape	
Nelson Mandela Hospital	1
Free State	

Universitas Academic Hospital	5
Total anticipated per year	**40**

The regimen of 500mg per dose at day 0 and day 14, repeated at 6 months is recommended as a means to contain associated costs.

Rituximab regimen	No. of patients	Cost per patient per cycle	Cost per patient per year	Budget Impact per cycle	Budget Impact per year
375 mg/m2/dose at 0, 1, 2, 3 weeks	40	R38,494.76	R76,989.52	R1,539,790.40	R3,079,580.80
750 mg/m2/dose at 0 and 2 weeks	40	R41,702.64	R83,405.28	R1,668,105.60	R3,336,211.20
500 mg/dose at 0 and 2 weeks	**40**	**R16,039.50**	**R32,079.00**	**R641,580.00**	**R1,283,160.00**
1000 mg/dose at 0 and 2 weeks	40	R32,079.00	R64,158.00	R1,283,160.00	R2,566,320.00

11. Recommendation

To prevent progression towards ESRD, rituximab is recommended in patients with refractory LN where conventional therapy has failed. It is recommended that access be restricted to nephrology centers and prescribed on a named patient basis. Therapy should be initiated as per the attached algorithm at a dose of 500mg administered at days 0 and 14, repeated 6 monthly dependent on clinical response. Treatment is only recommended when there is biopsy proven evidence of disease, with serological and biochemical markers of activity as well as demonstrated adherence to induction and maintenance therapy. Rituximab is not recommended for patients with advanced stages of kidney disease (GFR <15ml/min).

12. Monitoring and evaluation considerations:

It is also recommended that the use of rituximab be recorded in a biological's registry initiated by the local Pharmacy and Therapeutics Committees (PTC). The clinical outcomes should be shared with a national registry database for biological therapy.

Commented [JR1]: Provide the process

Review indicator:

Evidence of efficacy	Evidence of harm	Cost savings when compared to cost of dialysis (R200 000 per patient per annum)[3]
X	X	X

VEN status:

Vital	Essential	Necessary
		X

Evidence to decision Framework

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident [X] Not confident [ ] Uncertain [ ]	Trial data shows variability for clinical endpoints. Prospective observational data and clinical registries indicates consistent benefit. Evidence from studies and clinical registries indicate a cure rate ranging from 30-64% for refractory lupus nephritis
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms [X] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ]	Harm includes renal failure and reduced lifespan. Side effects/ adverse effects: adverse effects reported in studies include sepsis and infusion related reactions The desirable effects of preventing or delaying dialysis outweighs any potential adverse event that may be reported.
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes [ ] No [X]	This is rescue therapy for patients who have failed conventional treatments for their condition.
VALUES & PREFERENCES / ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [ ] Major [ ] Uncertain [X] **Is the option acceptable to key stakeholders?** Yes [X] No [ ] Uncertain [ ]	There is no acceptability evidence, so agree that this is uncertain. Although, given the alternative (renal failure, death) patients might value an option over nothing Key stakeholders Nephrology and Rheumatology units managing lupus nephritis
RESOURCE USE	**How large are the resource requirements?** More intensive [ ] Less intensive [X] Uncertain [ ]	Cost of medicines/ month: **Medicine** | **Cost (ZAR)** Rituximab | **R32,079.00** per once off course for 500mg dosage regimen **Prevention of Renal dialysis (+/- R200 000/year)*
EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [X] Uncertain [ ]	Access will be limited to those in tertiary institutions for their SLE nephritis treatment.
FEASIBILITY	**Is the implementation of this recommendation feasible?** Yes [X] No [ ] Uncertain [ ]	This is feasible to deliver through tertiary institutions with trained specialists managing the rare condition See summary for guidelines of implementation

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	☐	☐	☐	X	

References:

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[16] Porter A et al. Prospective long term follow up of the rituximab steroid sparing regimen in lupus nephritis NDT (2015). Vol 30: iii41.

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[20] Morrison, R. C. A. et al. Differences in systemic lupus erythematosus among 4 racial groups in South Africa. Arthritis Rheum, 33, S104. 1990

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