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Full Length Research Paper

Eculizumab as a therapeutic option for refractory lupus nephritis and lupus associated thrombotic microangiopathy: A review of current evidence

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Abstract

Lupus nephritis is a severe complication of systemic lupus erythematosus, leading to significant morbidity and mortality. The optimal choice and duration of therapy for lupus nephritis, especially in refractory disease and those associated with thrombotic microangiopathy, remains elucidated. The importance of complement activation in the disease process is gaining recognition; thus, complement blockade by eculizumab (terminal complement inhibitor) is advocated as a possible treatment option. This review summarises the latest evidence of eculizumabin treating refractorylupus nephritis with or without associated thrombotic microangiopathy. Eculizumab was successful in 19/22 cases of lupus nephritis, regarding dialysis cessation and improvement in clinical and biochemical parameters. However, there were significant complications such as nausea, vomiting, fungaemia and Streptococcus pneumonia infection. In conclusion, eculizumab might be an effective treatment for refractory lupus nephritis with or without thrombotic microangiopathy, but further clinical trials are warranted.

Key words: Eculizumab, complement, lupus nephritis, refractory, thrombotic microangiopathy.

INTRODUCTION

Lupus nephritis (LN) is a severe manifestation of systemic lupus erythematosus (SLE), an autoimmune disease caused by a loss of tolerance to self-nuclear antigen.[1] In LN, circulating autoantibodies interact with various nuclear antigens within glomerular cells and neutrophils and components of the glomerular basement membrane and mesangium, forming *in situ* immune complexes.[2,3] Complement activation, including C3a and C5a, is widely recognised in LN, with low levels of C3 and C4 present in 90% of people with diffuse LN.[4] The anaphylatoxins (C3a, C4a and C5a) are central in disease pathogenesis, leading to downstream effects such as phagocyte recruitment, vasodilation and mast cell-mediated histamine release. [5]Furthermore, it has been suggested that the epithelial side of the glomerular basement membrane lacks complement protective mechanisms, making it vulnerable to complement-mediated injury.[6] In class I to IV LN, the subendothelial or mesangial complement activation allows leucocyte infiltration, phagocytosis of the immune complexes, and further release of pro-inflammatory mediators, leading to chronic glomerular inflammation and renal injury.[7] In class VLN, antibody deposits and injures the podocyte, resulting in capillary wall lesion with proliferation and exudation, manifested phenotypically as membranous nephropathy.[7] Whilst complement has a significant role in the pathology

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of LN, the interplay of immune complexes, pro-inflammatory mediators and infiltrating cells, are also pertinent in the development and chronicity of LN.[8]
Current literature suggested that 17.5% of patients with LN develop Thrombotic microangiopathy (TMA) with normal ADAMTS13 levels and no identifiable Shiga toxin, resembling secondary atypical haemolytic uraemic syndrome (aHUS)[9, 10] It is postulated that secondary aHUS manifest as a result of complement dysregulation, catalysed by antibody-antigen interactions, which is prevalent in LN.[10]

Current treatment for lupus nephritis

Current treatment for LN mainly focuses on general immunosuppression with a reasonable level of success in achieving disease remission, as measured by resolution of symptoms clinically and biochemically, reducing proteinuria and urinary sediment and improving serum creatinine concentration.[11] The European League Against Rheumatism (EULAR) and European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) published a clear guideline for treatment, intending to achieve proteinuria <0.5g-0.7g/24 hours by 12 months, improved proteinuria by three months and ≥50% reduction in proteinuria by six months (figure 1).[12]

Refractory lupus nephritis

Refractory LN is defined as the failure to achieve proteinuria targets despite aggressive medication.[12] The treatment options for these patients include any induction agent or rituximab as monotherapy or adjunct.[13] Furthermore, high doses of immunoglobulins (2g/kg) can be considered instead of increasing glucocorticoids, while plasma exchange is rarely indicated nowadays.[12, 13]\l "As such, the optimal therapy for refractory LN remains undetermined; thus, investigators have been looking at alternative novel agents. Evolving theories hypothesised that inhibition of the complement cascade might attenuate renal injury.[4] Several case reports have described using the C5 complement inhibitor eculizumab in treatment-resistant LN patients. This review attempts to summarise the latest evidence of eculizumab as a treatment for refractory LN and LN-related TMA.

Eculizumab

Eculizumab is an IgG2/IgG4 humanised monoclonal antibody that inhibits the cleavage of complement C5 in the complement cascade, by binding to the alpha-chain of C5, thereby inhibiting the attachment of C5 convertase.[14] As a result, it prevents the formation of C5a and C5b, and the latter is an anaphylatoxin that leads to the generation of the membrane attack complex (MAC).[15] MAC is the basis of many diseases with defective complement regulation, such as aHUS and paroxysmal nocturnal haemoglobinuria (PNH), for which eculizumab is efficacious.[16-18]\l "
While much of the research involving eculizumab in the past has shown promising results, it should be noted that preventing MAC formation increases the risk encapsulated organisms infections. Hence patients receiving eculizumab treatment are required to have mandatory vaccination against encapsulated organisms, including Neisseria Meningitidis, with additional prophylactic treatment with penicillin V or ciprofloxacin until two weeks post-vaccination.[19] Furthermore, vaccination against the encapsulated organisms *Streptococcus pneumoniae* and *Haemophilus influenza* are also suggested for patients under 18 years old with certain risk factors.[20]

Eculizumab and refractory Lupus Nephritis

Like aHUS and PNH, the pathophysiology of LN also involves activation of the complement system, particularly C5a.[16] Thus, the use of eculizumab appears reasonable. In addition, several case reports used eculizumab as rescue therapy for refractory LN with encouraging results.[21] However, the efficacy might be confounded by including patients with refractory LN and associated pathologies, such as primary aHUS.

Early studies demonstrated that treating LN in mice with eculizumab for six months increased their survival and resolution of LN.[22] In the NewZealand Black/White (NZB/W) F1 mouse model, the use of recombinant protein inhibitors and genome-wide association studies have shown that complement plays an essential, but paradoxical role in the development of SLE and its complications.[22] The paradoxical part of the complement cascade is that deficiencies of the early pathway (C1q and C4) are associated with an increased risk of SLE, whilst patients with deficiencies of C3 show no association with SLE.[4]\l "\l "Additionally, patients with SLE often present with hypocomplementaemia, characteristically low C3 and C4.[23] As such, the complement cascade's initial components provide an essential, protective role in the clearance of apoptotic cells and immune complexes while the terminal components, from C5 onwards, are pro-inflammatory and associated with the tissue damage observed in SLE[4, 24]. As eculizumab inhibits complement binding to C5 convertase, it downregulates the complement cascade's pro-inflammatory components whilst maintaining the beneficial immune complex clearing initial components (figure 2).[25] This advantage of eculizumab has gained wide attention and trials into the potential role in LN treatment in humans.

Phase 1 trials have shown that eculizumab is safe and well-tolerated in patients with SLE. Unfortunately, there are no known phase II trials to date that have assessed the use of eculizumab in patients with SLE. Yet, three

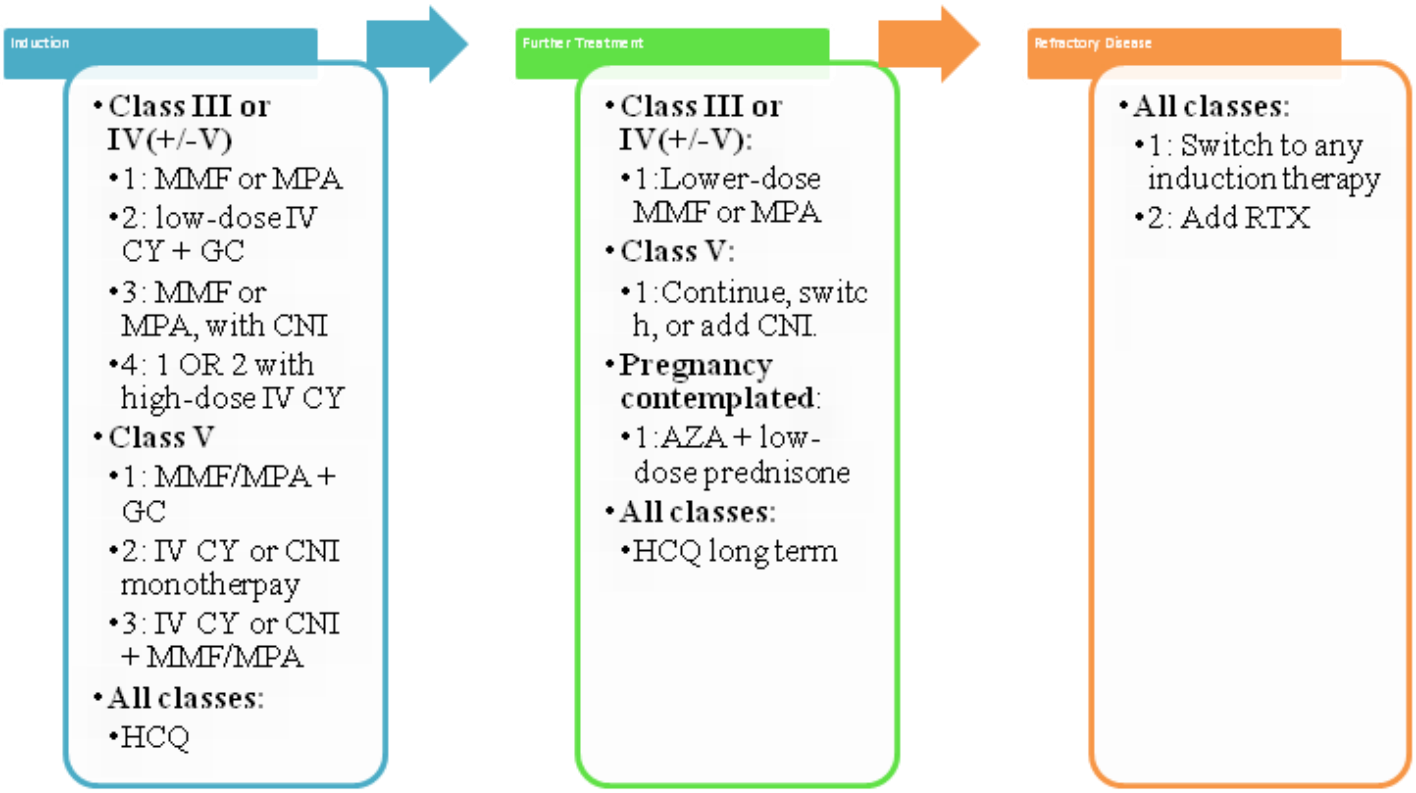

Figure 1. The treatments for induction, further treatment, and refractory disease in lupus nephritis. The induction phase considers two groups, class III or IV(+/-V) and a pure Class V LN. Different induction options can be considered in each group, as indicated by options 1, 2, 3 and 4. All patients receive HCQ. For further treatment, the same groups are considered, with the addition of patient's contemplating pregnancy. In refractory disease, regardless of the class, any treatment in induction can be considered. RTX can also be added to any of these schedules. IV, intravenous; AZA, azathioprine; CNI, calcineurin inhibitor; CY, cyclophosphamide; GC, glucocorticosteroid; HCQ, hydroxychloroquine; LN, lupus nephritis; MMF, mycophenolate mofetil; MPA, mycophenolic acid; RTX, rituximab.

phase II trials of patients with aHUS are available, demonstrating that eculizumab usage led to a reduction in terminal complement activity and improvement in haematological parameters.[26-28]\l "

Lupus nephritis with Thrombotic microangiopathy: Background

The combination of both LN and TMA contributes to more severe renal injury than LN alone, and is generally unresponsive to conventional therapy.[29] Case reports have shown that treatment with eculizumab is effective in patients with both LN and TMA.[30-32] While the precise mechanism of how LN unmasks TMA's is unclear, recent studies have noticed a complement driven pattern of the TMAs found in LN.[10] Park et al. distinguished these cases as complement-mediated TMAs (CM-TMA), due to their normal levels of ADAMTS13 and lack of Shiga toxin.[10] A recent proposition suggested that complement dysregulation in LN, including decreased C1q, C2-4, leads to activation of TMA.[33] Furthermore, biopsies from Cohen's study showed that C4d staining positivity in renal biopsy correlated with TMA occurrence, indicating a possible role of the classical pathway to develop TMA in LN.[34] Chau et al. showed that C4d is ubiquitously found in their TMA patients, and more than 75% of patients also had C5b-9 deposits present.[35] Together these findings provide a solid basis for terminal complement system activation related to TMA in LN patients.

Furthermore, C4d and C5b-9 deposits may not be the only manifestations of TMA in LN patients. Song et al. proposed that alongside complement deposits, decreased serum complement factor H (CFH) may have a basis in TMA development.[36] It is thought that reduced factor H found in LN leads to damage of erythrocytes, consumption of platelets and eventually development to TMA.[37] Recent studies have proposed that this reduction in CFH is related to monomeric C-reactive-protein (mCRP), which forms during renal injury. One role of mCRP is to bind to CFH and enhance its cofactors. However, autoantibodies against mCRP prevent this process and are postulated to cause CFH depletion and the overactivation of the complement system.[38] Interestingly, Chen et al. showed that 92% TMA occurred after SLE development, further supporting the defective complement system in LN may be the culprit of subsequent TMAs.[39]

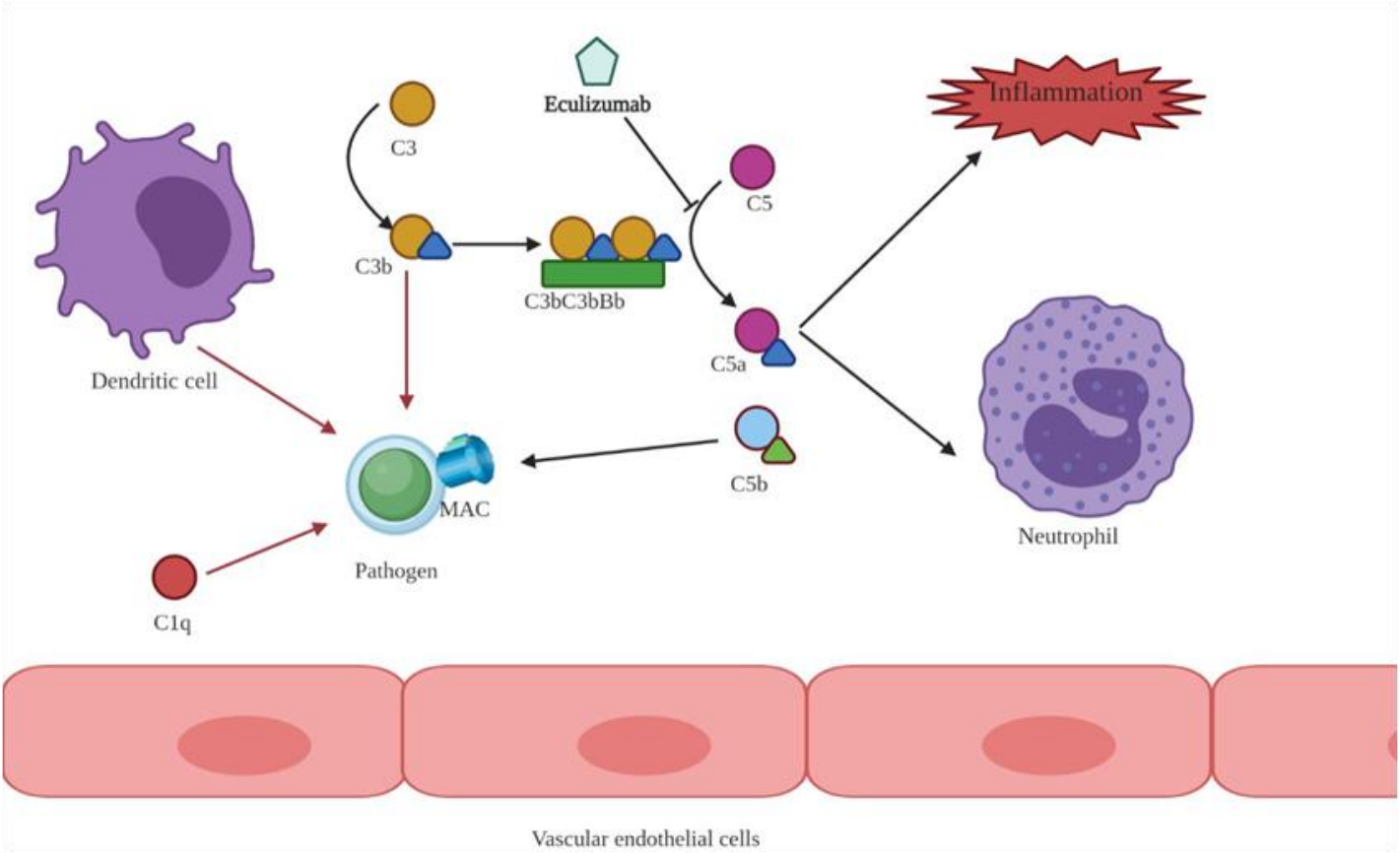

Figure 2. C3 is formed into C3b, which can then opsonise pathogens. C3b is converted to C5 convertase (C3bC3bBb), which cleaves C5 into C5a and C5b. C5b initiates the assembly of the membrane attack complex (MAC). C5a acts as a potent inflammatory mediator, triggering immune cell recruitment. C1q also opsonises pathogens, allowing phagocytic macrophages and dendritic cells to remove them.

Current evidence of Eculizumab in SLE related TMA

To date, we identified 9 case series on eculizumab for the treatment of LN with associated TMA. The OVID and PubMed data bases were used with search term including: 'resistant lupus nephritis', 'systemic lupus erythematosus'; 'thrombotic microangiopathy', 'atypical haemolytic uraemic syndrome'; and 'eculizumab'. We included studies up until 2019. Reports that were included were those with refractory LN, or those who had no response to conventional treatment of LN. Studies that were excluded were those with antiphospholipid antibody syndrome, and thrombocytopenic thrombotic purpura.

The studies' characteristics are summarised in table 2. Six out of the nine reported cases had only single patients. Whilst three studies, Bermea et al., Park et al.,and Cavero et al., observed 2, 11, and 27 patients, respectively.[10, 40, 41] Altogether there were 48 patients in the nine-case series. 41% were females with ages ranging between 4 and 59 years. Most patients underwent kidney biopsy. There was only one class II LN and one class V LN, whilst all others were class III or IV.[30, 40] Eight out of the nine-studies measured ADAMTS13 and showed normal activity. Although Hadaya and colleagues did not measure ADAMTS13, they confirmed TMA on biopsy with complement deposition, similar to Pickering and colleagues.[31, 42]

As illustrated in figure 1, before eculizumab commencement, 7/9 case reports utilised rituximab, as suggested by the EULAR 2019 guidelines. One patient had a kidney transplant during treatment with eculizumab. In all cases, the lack of clinical improvement after the commencement of rituximab led to the initiation of eculizumab treatment. 44% of patients followed the Food and Drug Administration approved schedule: 4 weekly doses of 900mg IV followed by 1200mg IV every second week. 22% ceased treatment early due to rapid recovery.[31, 40] One study involved a paediatric patient, and eculizumab was dose adjusted by weight.[43] Pickering and colleagues commenced eculizumab at 1200mg IV weekly for four weeks, whilst El Husseini and colleagues initiated at 1200mg IV fortnightly.[30, 42] All studies continued eculizumab at 1200mg fortnightly, until discontinuation. Patients were treated between 2 weeks to 20 months.

Following eculizumab therapy, 86% (19/22) of patients with LN showed remission of TMA. Eculizumab was discontinued when there was sustained clinical response

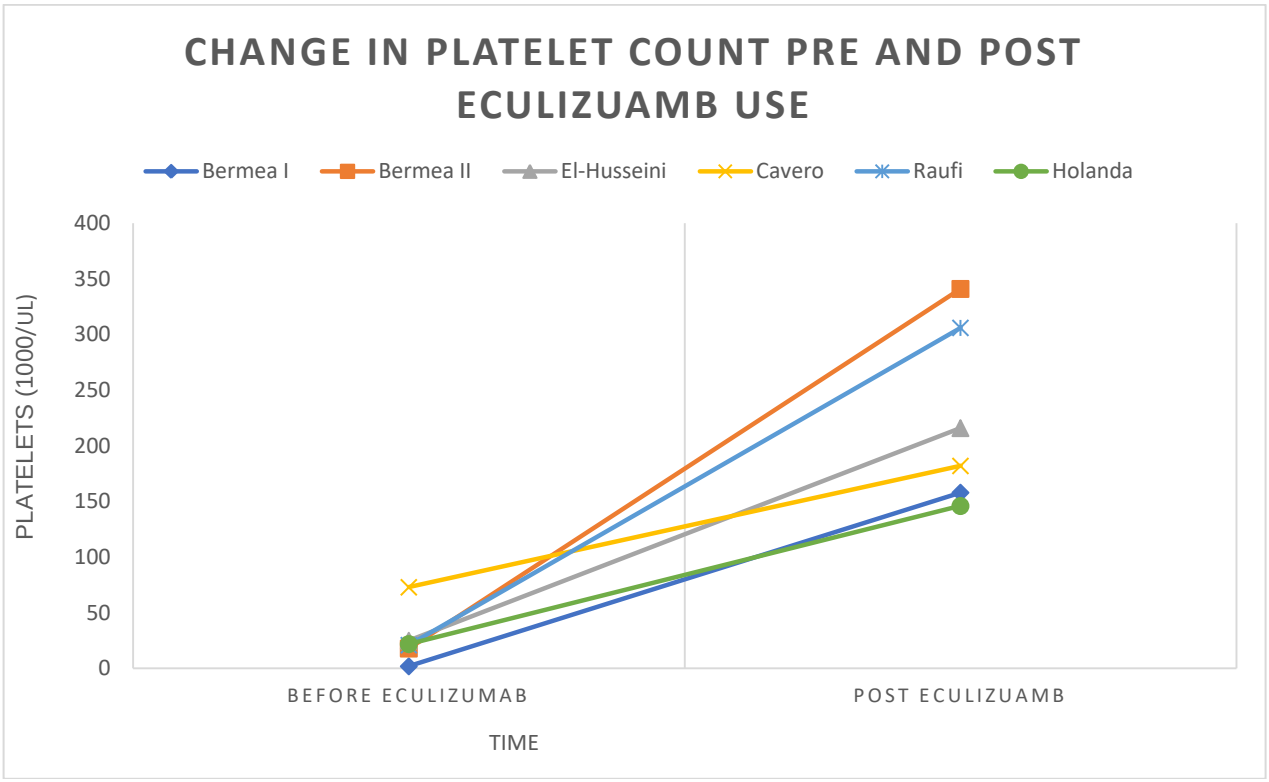

Figure 3. Change in platelet count, pre and post eculizumab use.

and biochemical improvement, with the range of eculizumab use being between 2 weeks and 20 months. Some studies also showed discontinuation of dialysis after eculizumab therapy. Of the seven patients on dialysis in Park et al., four discontinued dialysis treatment acutely, whilst one ceased peritoneal dialysis at 36 weeks post eculizumab.[10]In Hadaya's study, dialysis was commenced as an adjunctive treatment, but was terminated by the third dose of eculizumab.[31]The exception was Cavero et al., where none of their three SLE patients benefited from eculizumab.[41] One patient received a kidney transplant.[31]

The primary biochemical outcomes highlighted were platelet count, serum creatinine and urine protein/creatinine ratio. Such trends are summarised in figures 3 to 5 respectively. Other outcomes included C9 staining and dialysis discontinuation. In essence, these parameters showed significant improvement after eculizumab treatment.

Infection is a significant adverse effect of concern. Whilst appropriate meningococcal vaccine and prophylactic antibiotics were given to patients in all studies, three out of nine studies reported infection during the use of eculizumab. The first was Park et al., who report mortality due to disseminated fungal infection. The authors attribute this to prolonged high dose corticosteroid use in LN, given that eculizumab was used only once.[10] The second was in Coppo et al., where their patient developed a Streptococcus pneumoniae pneumonia. Eculizumab was ceased, and the patient was treated with Meropenem. Three weeks following cessation of eculizumab, the patient's haematological condition worsened. Eculizumab was reintroduced; the patient did not have any further infective complications, and stable remission of LN was reported.[43] The third was in Cavero et al., where two kidney transplant patients developed prostatic abscess and herpes zoster, respectively. However, it was believed that these infections were related to their background immunosuppressive treatment.[41]

DISCUSSION

TMA is a syndrome characterised by thrombocytopenia, microangiopathic haemolytic anaemia with the presence of schistocytes, and organ-specific dysfunction manifested by clinical or laboratory abnormalities .[44]Although TMA is a relatively rare condition, it has a higher correlation with SLE patients than the general population. One biopsy study of 342 patients with LN in China found TMA in 17.6%, whilst a recent review reports TMA to be found in 8-15% of SLE patient biopsies.[45, 46]Compared to other renal vascular lesions, TMAs result in the worst renal outcomes.[46] These patients also have a higher rate of treatment failure than patients with other or no renal vascular disease.[46] These findings are reinforced by Park et al., who reported 11 patients with TMA in LN, resistant to conventional therapy.[10] Despite this, the use

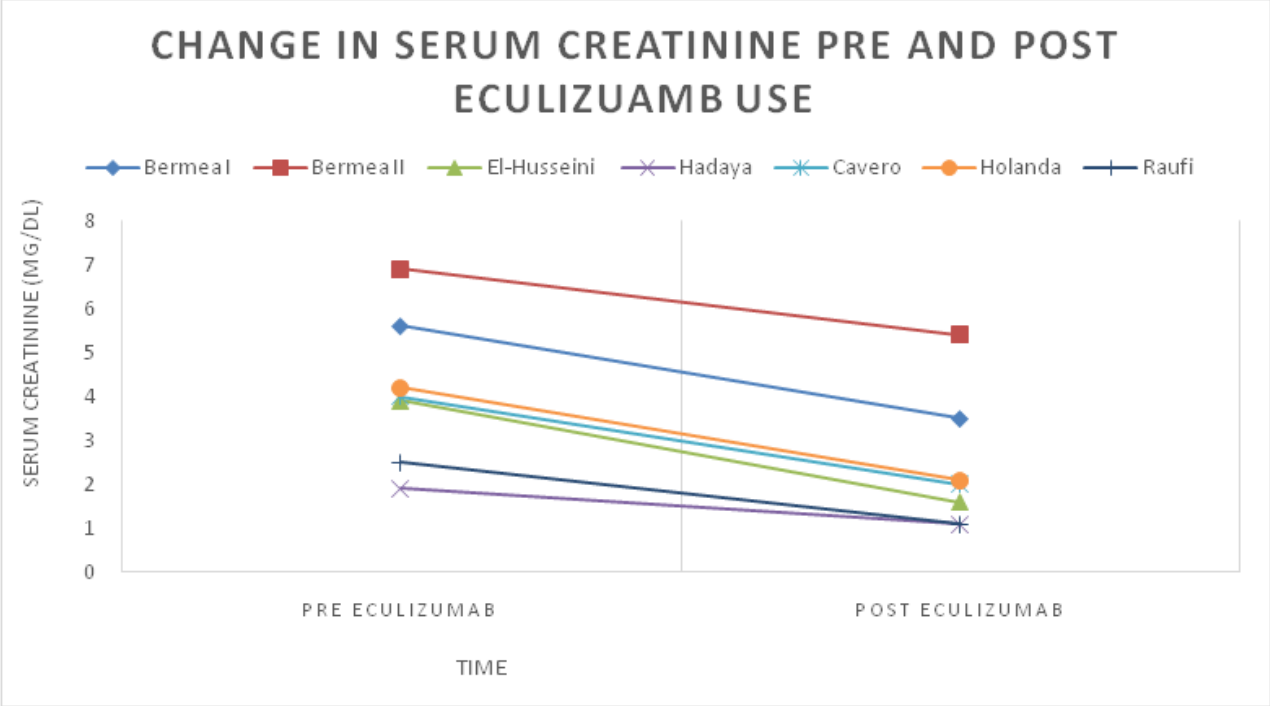

Figure 4. Change in serum creatinine, pre and post eculizumab use.

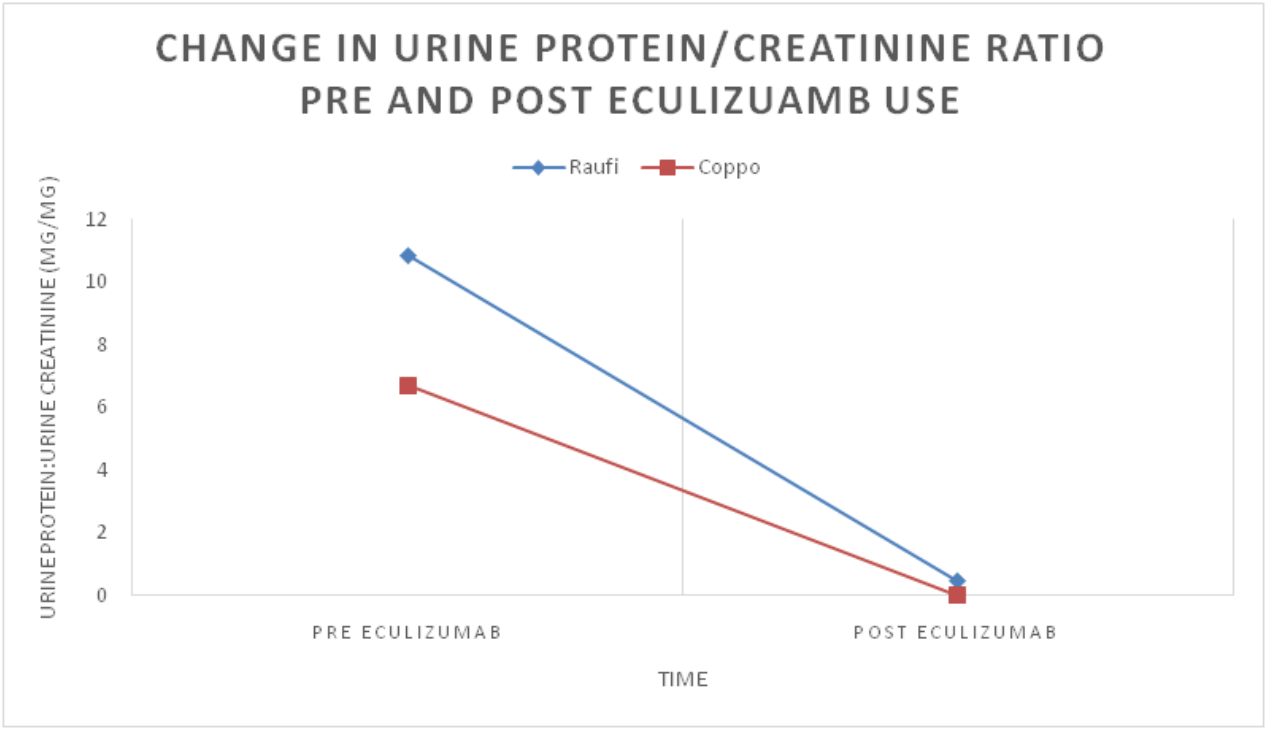

Figure 5. Change in urine protein: creatinine, pre and post eculizumab use.

of complement inhibitors in TMA associated LN is still developing. This review summaries 9 case reports of patients presenting with refractory LN, associated with CM-TMA, treated with eculizumab. To our knowledge this is the first review to examine the role of eculizumab in refractory LN with and without CM-TMA. In our review, we excluded secondary TMA in conditions such as antiphospholipid antibody syndrome, as there is some

Table 1. Patient characteristics of 9 case series and reports.
Legend: Plt=platelet 1000/µl, sCr= Serum Creatinine (mg/dl), eGFR= estimated glomerular filtration rate (ml/min/1.73m^2), SLE= systemic lupus erythematosus, LN= Lupus Nephritis, aHUS= atypical haemolytic uraemic syndrome, APLS= antiphospholipid antibody syndrome, M= male, F=female, CM TMA= Complement mediated Thrombotic microangiopathy.
[a]Median(25-75th percentile)

Author	Patient population: Age(years), Sex, Ethnicity	Indication	Outcomes	Side effects: infection, allergy, complications	Others: pregnancy, Transplant
Coppoet al., 2015.	Age 4, Female Moroccan	SLE: Class IV-G lupus nephritis.	Stable remission	Retrocardiac pneumonia; streptococcus pneumonia	Child
Cavero et al.,2017	Age: 51.8(36.2-59.6)[a] 16/29 Male.	'Secondary aHUS.' Total: 29 Drug-induced: 15 Systemic: 8 (SLE=3; Scleroderma=2; Vasculitis=2; APLS=1) Postpartum: 2 Cancer: 2 Acute humoral rejection: 1 primary intestinal lymphangiectasia: 1	10/14 no dialysis 25% decrease SCr in 20/29 eGFR>60 ,10/29	Infection in 2/7 kidney transplant patients.	7 Transplant Two postpartum 2 Malignancy
Bermea et al., 2016	Age 30, Female African American SLE	Patient 1 Class III Approaching class IV.	Haemodialysis dependant. Clinically improved	Nausea and vomiting.	
	Age 21, Male, Hispanic	Patient 2 Class II LN.	Haemodialysis dependant Nil thrombocytopenia Clinically improved	Nausea and vomiting	
Pickering et al. 2015	Age14, Female, Caucasian		Biopsy 18mo post: C9 stain minimal No necrosis		
Raufi et al., 2016.	Age25, Female, Vietnamese	Diffuse proliferative LN IV		-	-
De Holanda Barbosa et al., 2017	Age 18, Female,	Class IV Dysuria, skin rash, oligo-anuria	Dialysis discontinued	-	

		Uremic symptoms			
El-Husseini et al., 2014	Age 24, Female African American	Class V lupus nephritis		Acute hypoxia respiratory failure	
Hadaya et al., 2011	Age 27, Female	End-stage renal failure Complete glomerular scaring and diffuse tubulointerstitial fibrosis	Biopsy: the resolution of TMA. Dialysis discontinued.		Kidney Transplant
Park et al., 2018	n=11 Age: 22-59[a],	CM TMA and LN	4/10 discontinued dialysis One death (disseminated fungal infection)	Fungaemia APLS in 3	

evidence of eculizumab effectiveness in this group. [47] In the case series we identified, most patients treated with eculizumab showed complete recovery of haematological parameters.[10] There is a new emerging role of complement inhibition therapy in CM-TMA, especially in patients resistant to conventional treatment.[48]

A variety of parameters were used to indicate progression of LN, with the most common being platelet

Table 2. Summary of clinical and biochemical parameters of patients pre and post eculizumab treatment, in 9 studies.
Legend: CS= Corticosteroid, Cyc =cyclophosphamide, CYSP= Cyclosporine, HCQ=hydroxychloroquine, HD= haemodialysis, Methotrexate= Mtx, Mycophenolate mophetil= MP, Rtx=Rituximab, PE=Plasma Exchange, Tacrolimus= Tac Platelet= 1000/μl, , eGFR=estimated glomerular filtration rate (ml/min/1.73m^2) , APLS= antiphospholipid antibody syndrome, ADAMTS13= a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13.

Author	Therapy pre eculizumab	Last recorded renal and haematological parameters pre eculizumab	Dosing and times	Earliest reported signs of recovery	Duration	Renal and haematological parameters post Eculizumab	Side effects and complications during treatment
Coppo R, 2015.	CS, Cyc, CYSP,IV MP, MMF, Rtx.	eGFR:28 Platelet: 55 UP/UCr:8	300mg(20mg/kg) , fortnightly.	Rapid	17 months.	eGFR > 12 Platelet> 150 UP/UCr:0	Retrocardiac pneumonia; streptococcus pneumonia
Cavero et al., 2017	Drug induced: 13=PE; Systemic (8): 8CS, 5Cyc, 1MMF, 1RTx,5 PE; 1 Mtx; Other(6): 1CS, 1 IVIG,1 Rtx, 6PE	eGFR: 18 Platelet: 65 serum creatinine: 3.5	900mg/week for four weeks IV. Then 1200mg/ fortnight	Rapid	8 weeks (median)	eGFR: 34 Platelet: 182 serum creatinine: 2	Infection in 2/7 kidney transplant patients.
Bermea (2016)	CS, Cyc,Rtx, PLEX, HD	.	900mg IV x4 and then 1200mg/fortnight	Within 44 days	6 months.	Platelet: 158 serum creatinine:3.6	Nausea and vomiting.
Bermea(2016)	CS,Cyc,Rtx, PLEX, HD,	Platelet: 36 serum creatinine:	900mg weekly	Rapid (≤2 days)	2 weeks	Platelet: 341 serum	Nausea and vomiting

	HCQ	6.9mg/dl				creatinine:5.4mg/dl	
Pickering et al. 2015	Cyc, MMF, Rtx,Tac	-	1200mg/week x4 1200mg/fortnightly x2	≤7 days	2 months.	Biopsy 18mo post: C9 stain minimal No necrosis	-
Raufi et al., 2016.	CS, Cyc, MMF,Rtx, PE	Platelet: 21 UP/UCr:10.84 serum creatinine:2.5mg/dl	900mg./ week x4 1200mg/fortnight. x21	Immediate	25 weeks	Platelet: 306 UP/UCr: 0.46 serum creatinine:0.9 mg/dl	-
De Holanda Barbosa Et al., 2017	CS, Cyc, MMF, Rtx, PE	Platelet 22 serum creatinine: 4.2	900mg/week x 4 1200mg fortnightly.	≤7 days	-	Platelet: 33.2 serum creatinine: 2.1mg/dl	-

count, serum creatinine, urine protein/creatine ration, haemoglobin, haptoglobin, and LDH. Reported cases show that the use of eculizumab improved platelet count and renal function, including proteinuria. However, one of the case series did not show any improvement despite eculizumab.[41] The authors suggested that this may be due to longstanding disease, with biopsies showing severe lesions before treatment. This means that late treatment administration is expected to have a less pronounced effect and indicates the importance of early treatment with eculizumab when refractory LN is identified.

So far, there has been limited research into the role of eculizumab in refractory LN. The definition of refractory

Table 2. Cont.

El-Husseini 2014	CS, Cyc, PE	eGFR:19 Platelet: 25 serum creatinine:6.4 UP/UCr:4.9	1200mg fortnightly	≤7 days	6 months	eGFR:47 Platelet: 216 serum creatinine:1.6 UP/UCr: 1.6	Acute hypoxia resp failure
Hadaya 2011	Rtx, Transplant, thymoglobulin	serum creatinine:1.95	1200mg/week	Immediate	Five weeks	serum creatinine: 1.15	-
Park, 2018	CS, PE, immune-modulatory therapy.	Platelet: Median: 60 Range: 8-160	900 mg /week x4 1200 mg/fortnight	Immediate	Mean: 82.2 Median of 63.5 Range, 7-190 weeks	PlateletMedian: 170 Range: 96-320	Fungaemia APLS x3

lupus nephritis has considerable variability amongst nephrological societies.[49] EULAR/ERA-EDTA suggest the definition of a failure to achieve protein urine goals within 12 months, but this definition is difficult to apply in many studies.[12] The main challenges in its definition are that: 1. it is unclear when first to assess protein parameters; 2. reaching clinical response does not equate to having any activity on biopsy; and 3. compliance with medication impacts the duration of treatment.[50]

No studies to date have been able to identify eculizumab with 'refractory LN'. However, the search amongst systematic reviews has explored the use of eculizumab in disease unresponsive to conventional therapy.[51] Early initiation of eculizumab in patients with CM-TMA seems desirable, but currently, there is no established guideline to demonstrate the timing of drug use. All the reported cases commenced eculizumab after exhausting conventional therapies.

The longest follow up was three years after initiating eculizumab.[52] On the last follow-up, the authors reported no signs of TMA on repeated biopsy and improved serum creatinine, reduced proteinuria, and improvements in parameters such as platelets and haemoglobin. Findings from 9 case reports suggest the utility of eculizumab in refractory LN with CM-TMA. Thus, eculizumab seems to have a role in the management of complement-mediated diseases such as LN. However, although its efficacy can be appreciated, further studies would be needed before incorporating it into clinical practice.

Currently, \l "\l "\l "\l "\l "\l "there are no universally standardised parameters for monitoring eculizumab therapy in CM-TMA; the decision to discontinue treatment remains challenging, especially in LN associated TMA.[53] Eculizumab was ceased based on clinical response and improvements in renal parameters.

Nonetheless, pharmacokinetic studies have suggested that complement activity (CH50) and alternate pathway activity (AP50) may be appropriate to measure eculizumab effectiveness, although AP50 is not entirely suppressed even at high doses of eculizumab. [54] Current studies suggest that if discontinuation is considered, close monitoring of standard laboratory parameters (platelets, creatinine) and potentially assays (CH50, AH50, sC5b-9) should be used to ensure disease remission.[55] However, the most extended length of eculizumab use in these case reports was 20 months. Thus, further longitudinal studies would be ideal for monitoring disease relapse.

Currently there are no guidelines recommending the use of eculizumab in LN with CM-TMA. Findings from our review suggest if CM TMA is suspected, patients may benefit from early commencement of eculizumab. In all the reported cases, eculizumab was not commenced until patients were deemed refractory to current conventional treatment i.e. rituximab and plasma exchange, further indicating the difficulty of the diagnosis. Nonetheless, it remains appropriate to follow the EULAR guidelines for initial investigations. Guidelines recommend early investigation with renal biopsy, and testing for antiphospholipid antibody syndrome. [56] The presence of TMA lesions on biopsy is not pathognomonic, and guidelines appropriately suggest considering conditions that have a similar histopathological overlap including Thrombotic thrombocytopenic purpura (TTP), HUS, malignant hypertension and complement mediate TMA. [36] Prompt and early investigation to rule out these conditions is imperative. There is strong evidence for the early use of eculizumab in aHUS, and our review also supports early initiation of eculizumab in CM TMA. [27]. However, future controlled studies are required to guide definitive use and recommendations of eculizumab in LN caused by CM-TMA.

Limitations to this study were publication bias, sample size, and comparability of parameters. Firstly, publication bias may exist, as studies are less likely to be reported on eculizumab failure. Secondly, the study is limited by

case reports available due to the low prevalence of the LN associated complement-mediated TMA. Finally, serological and non-serological parameters throughout the case series varied, which reduced the ability to appreciate the effect of eculizumab and provide further statistical analysis.

CONCLUSION

Eculizumab might be a potential effective rescue treatment for patients with refractory lupus nephritis and LN with TMA, with an acceptable adverse effect profile. However, we need further studies to evaluate its long-term efficacy. Future guidelines should consider including eculizumab as one of the treatment options in the management of lupus nephritis, especially in patient's refractory to conventional treatment or in patients with lupus nephritis and associated thrombotic microangiopathy

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