Autoimmunity Reviews 18 (2019) 510–518

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Refractory lupus nephritis: When, why and how to treat

Andreas Kronbichler[a,b,1], Biljana Brezina[a,1], Philipp Gauckler[b], Luis F. Quintana[a,c], David R.W. Jayne[a,d,*]

[a] Vasculitis and Lupus Clinic, Addenbrooke's Hospital, Hills Road, CB2 0QQ, Cambridge, Cambridge University Hospitals, United Kingdom
[b] Department of Internal Medicine IV (Nephrology and Hypertension), Medical University of Innsbruck, Anichstraße 35, 6020 Innsbruck, Austria
[c] Servicio de Nefrología y Trasplante Renal, Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi I Sunyer (IDIBAPS), Universidad de Barcelona, Barcelona, Spain
[d] Department of Medicine, University of Cambridge, CB2 0QQ Cambridge, United Kingdom

ARTICLE INFO

Keywords:
Lupus nephritis
Multi-target
Rituximab
Immunoadsorption
Transplantation
Bortezomib
Refractory
Treatment

ABSTRACT

Refractory lupus nephritis indicates an inadequate response to lupus nephritis therapy. It implies persisting or worsening disease activity despite therapy, but the definition is complicated by the parameters of response, proteinuria and renal function, that do not discriminate clearly between activity and irreversible damage. Understanding the causes of refractory disease and developing treatment strategies is important because these patients are more likely to develop poor outcomes, especially end stage renal disease. This review explores current concepts and definitions of refractory disease and summarises treatment approaches that have been used in observational cohort studies and case series. We highlight the importance of optimising adherence to the prescribed immunosuppressive and supportive measures and avoidance of diagnostic delay. Treatment options include higher dose glucocorticoid, switching between cyclophosphamide and mycophenolate acid derivates, or addition of rituximab, the latter potentially in combination with belimumab. Less evidence supports extracorporeal treatment (plasma exchange or immunoadsorption), calcineurin inhibitors (cyclosporine A or tacrolimus), intravenous immunoglobulin and stem cell transplantation. Improvements in understanding what refractory disease is and how definitions can be integrated into treatment pathways has the potential to enhance lupus nephritis outcomes.

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease, resulting from auto-immune dysfunction, and presenting with immune complex-mediated lesions of blood vessels in diverse organs [1]. Virtually any organ system can be affected; however, clinical symptoms are usually related to cutaneous, renal, neurologic, and haematologic presentations. Patients with both lupus and renal involvement (nephritis) do not represent a clear subset with respect to other manifestations, although Cervera et al. [2] showed that these patients have less skin and joint involvement, when compared to patients without nephritis.

Lupus nephritis (LN) is the most frequent severe organ manifestation of SLE. The clinical presentation is dominated by the presence of proteinuria (> 0.5 g per day) or a urinary protein/creatinine ratio (UPCR) of > 0.5 (mg/mg) or urinary protein > 3+ by dipstick analysis [3]. ACR lupus classification criteria also mandate presence of active urine sediment of more than five red blood cells per high-power field. However, "silent LN" can occur in the absence of either of those markers and renal biopsy is necessary to confirm renal involvement in these subjects [4,5]. Presence of "silent LN" may be responsible for the protective effects of ACE-inhibitors to prevent onset of LN [6]. If untreated, LN remains a major cause of ESRD and is associated with increased mortality and morbidity in patients with SLE. With the use of immunosuppression, the aim is to preserve kidney function and improve survival. This has been successful for most patients with LN. Unfortunately, a subset of LN patients fails to respond to immunosuppression remain refractory and are a management challenge with a high risk of a poor outcome.

There is no consensus definition of "refractory" LN, but the term implies an inadequate or no response to the remission-inducing treatment. Because remission is defined by reduction of proteinuria and stability or improvement in renal function it can be hard to discriminate treatment refractoriness from irreversible damage where these

* Corresponding author at: FMedSci, Professor of Clinical Autoimmunity, Department of Medicine, University of Cambridge, CB2 0QQ Cambridge, United Kingdom.
E-mail address: dj106@cam.ac.uk (D.R.W. Jayne).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.autrev.2019.03.004

Available online 04 March 2019

Table 1
Examples of definitions for refractory lupus nephritis.

Definitions
#1 Failure of at least one immunosuppressive drug [7–9]
#2 Failure of at least two immunosuppressive drugs [10]
#3 Poor response to at least one immunosuppressive drug [11]
#4 Failure to respond to immunosuppressive therapy including cyclophosphamide [12]
#5 Failure to respond to the combination of any immunosuppressive drug and corticosteroid therapy for at least 6 months [13,14]
#6 Failure to respond following treatment with mycophenolate mofetil or cyclophosphamide [15]
#7 Refractory to 'standard' treatment [16]
#8 No response to 'standard' treatment [17]
#9 Refractory to established therapy including high-dose corticosteroids and immunosuppressants [18]

outcomes are unachievable, and this dilemma permeates the literature. Thus, those with late or advanced presentations may not have the potential for remission by these criteria and are incorrectly judged to be non-responsive and refractory. Ideally, a repeat renal biopsy is required to determine whether or not activity persists.

Geographic, genetic and other epidemiological factors influence treatment response and renal outcomes and there is still variance in choice of initial treatments. It is becoming clear that the choice of a specific treatment agent is less important than understanding the nature of a treatment response, the safety of therapy and the need to identify treatment failure and move to alternative agents.

This review aims to elaborate on the series of available definitions of refractory lupus and to summarise the current knowledge obtained from observational studies introducing biologics in its treatment. Finally, it will hammer out potential applications of currently available treatment options in the context of refractory LN.

2. Definitions used in the assessment of lupus nephritis

There is no clear definition for refractory LN. Many attempts have been made to define refractory renal disease which are summarised in Table 1.

However, in order to optimise management of LN, which aims to offer long-term preservation of renal function and prevention of renal flares, recommendations or guidelines have been published by a combined task force of the European League Against Rheumatism (EULAR) and European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) [5], as well as by the American College of Rheumatology (ACR) [3] and the Kidney Disease International Guideline Organisation (KDIGO) [19]. The definitions for complete response, partial response and sustained response are also part of the guidelines discussed by the European expert consensus group, as part of the management of LN [5,20]. The EULAR/ERA-EDTA guidelines define refractory disease as failure to improve within 3–4 months, not achieving partial response after 6–12 months, or complete response after 2 years of treatment.

Complete response, which can take up to three years to achieve, is characterised by an inactive urinary sediment, a decrease in proteinuria to < 0.5 g/day and normal or stable (within 10% of normal GFR) renal function [21]. For these patients, the new ACR recommendations suggest continuation with the chosen induction regimen for another six months before considering change in treatment [3]. Partial response is a level of improvement, usually achieved after six to twelve months, and is characterised by presence of inactive sediment, > 50% reduction in proteinuria, normal (within 10% of normal GFR) renal function [22], and reduction to non-nephrotic proteinuria (< 3–3.5 g/d) if patients have been proteinuric before initiation of immunosuppression [23]. Defining response by proteinuria or by repeat renal biopsy may result in discrepancy as a significant proportion of apparent "non-responders" have inactive histology on follow-up biopsy [24,25].

A definition of refractory disease should embrace three dimensions: (1) failure to achieve a target in parameters reflecting disease activity; (2) drug exposure; and (3) period of observation.

The therapeutic approach for a patient who does not achieve remission, and this is attributable to active disease, is a switch of induction treatment after six months, from CYC to MMF, or vice versa [5,26]. More recently, B cell-targeted therapy with rituximab has shown high remission rates in patients with refractory LN, although a clinical trial failed to show additional benefit of rituximab on top of MMF in the treatment of immunosuppression-naïve LN patients [27]. Additional therapeutic options are emerging, such as other biologics, plasma exchange (PLEX), immunoadsorption (IAS), calcineurin inhibitors or eventually stem cell transplantation, discussed below.

3. Factors to consider in refractory lupus nephritis

Several factors can contribute to refractory disease. These include adherence with medication, tolerability of therapy and adverse events, a late presentation when irreversible disease may predominate, and true lack of efficacy of the induction regimen.

Several studies have explored non-adherence to medication in patients with SLE. Ward et al. [28] studied patient participation in the consultation and treatment efficacy in SLE and found less organ damage in the long term as a result of the better doctor-patient interaction with active patient participation. Petri et al. [29] examined the compliance with treatment and percentage of protocol visits kept in a mixed race cohort of 198 patients from which 115 were black and 83 white and concluded that non-compliance was a significant factor in determining renal morbidity (severe renal disease being defined as creatinine level 1.5 mg/dl or greater, renal failure, or nephrotic syndrome). In addition, black patients were twice as likely as white patients to have renal disease and were also more commonly classified as non-compliant (56%) than white patients (34%), which further highlights the importance of a patient-doctor interaction to improve adherence to prescribed medication. The French study group [30] identified a target trough blood hydroxychloroquine level of below 1000 ng/ml as a predictor of flare and this was attributed to poor adherence to treatment. Treatment related adverse effects can lead to reduced dosing and lack of efficacy. Certain drugs, including mycophenolate mofetil (MMF) and azathioprine, can be monitored by blood levels of the active drug or its metabolites in this situation. Investigation into the reasons for non-adherence may lead to improved control or a decision to switch to and alternatives should be considered if suboptimal dosing is likely to continue. Serious adverse events are frequent in LN and may be treatment related or unrelated, but whatever the cause they may result in interruption of effective therapy and loss of disease control. As discussed above, ongoing disease activity in the kidney can be hard to differentiate from irreversible damage and without a renal biopsy an assumption of active disease resistant to therapy may be incorrectly made.

Early diagnosis of renal involvement in SLE results in better treatment response due to less advanced activity and less irreversible damage. Accordingly, delayed diagnosis is more likely to lead to refractory LN. Presence of some or all of the risk factors for renal disease such as proteinuria, erythrocyturia or hypertension should and need to be considered early to prevent inflammatory lesions from their progression to sclerotic ones present in the end stage of LN. Determining the class of LN by performing kidney biopsy will help guide therapy and improve long term prognosis.

Optimisation of immunosuppressive dosing for a poor therapeutic response can include increasing the dose, for example of MMF to 3 g/day, or switching to enteric coated mycophenolic acid, which has been more successful especially in patients with reduced renal function [31]. There is limited experience of low dose, EUROLUPUS [32], cyclophosphamide dosing outside Northern Europe, and there is the possibility that higher cyclophosphamide doses will have higher response rates in

certain subgroups. Regimens with higher dose oral glucocorticoids or repeat dose intravenous methyl prednisolone pulses have had higher response rates at the cost of more glucocorticoid related toxicity [33]. With increasing use of lower glucocorticoid dose regimens, 'refractory disease' will be more common.

4. How to treat refractory lupus nephritis?

The EULAR/ERA-EDTA recommendations suggest a switch of either cyclophosphamide (CYC) to MMF or vice versa for refractory disease. This recommendation yielded a high agreement, but clear evidence to suggest such recommendation is missing. In addition, a switch to B-cell depletion with rituximab may be considered [5]. In a multicentre retrospective series of patients with either refractory or relapsing LN from Europe, a high response rate (87%) was reported following initiation of MMF. Notably, a majority of patients (73/85) were treated with CYC before MMF was commenced [34]. A single centre study from the United Kingdom including refractory patients with a majority having CYC in the past and kidney involvement reported a significant decrease in the corticosteroid dose, SLE disease activity index (SLEDAI) and proteinuria after initiation of MMF [26]. One has to be aware of racial and geographic disparities which may have an impact on refractoriness as has been shown in the response rate in the ASPREVA Lupus Management Study (ALMS) trial [35].

4.1. CD20-targeted therapies – Rituximab and novel strategies

Despite the failure of a randomised controlled trial comparing the addition of rituximab to MMF and steroids to standard of care treatment (placebo with MMF and steroids) [36] to demonstrate statistical superiority in response rates, rituximab has shown encouraging results in the treatment of refractory LN. This holds true for several different ethnicities and for diverse definitions of refractory LN reported so far. For the former assumption, some of the recent cohort studies are listed below.

In a Mexican cohort, ten out of 13 patients showed a response following rituximab treatment with a decrease of urinary albumin excretion from 3.3 ± 3.1 g to 0.4 ± 0.6 g per day after six months [7]. Another monocentric series indicated a therapeutic response in 12 out of 22 patients who received 2 doses of 0.5–1 g rituximab. Of note, the follow-up time of 3months was too short for a final analysis. One patient died due to invasive histoplasmosis during follow-up [8]. A renal response rate of 64% was reported in a Colombian cohort with refractory LN following B-cell depletion. Importantly, the number was lower (45%) when creatinine clearance was included in the assessment of renal response [9]. In a Singaporean cohort, administration of rituximab ($2 \times 375\,mg/m^2$) was accompanied by two pulses of CYC (500 mg each). All patients with renal involvement achieved a response towards this combination therapy with a decline of median proteinuria from 4.9 g to 1.0 g per day. An overlooked impact on healthcare economy following rituximab treatment was addressed by the authors, since they reported on a reduction of hospitalisation days from a median of 17.1 prior rituximab treatment to 0 during an observation period of 28 months following rituximab [10]. In a Korean multi-centre report eleven out of 17 patients showed a partial response following rituximab therapy and the SLEDAI score decreased from 11.9 ± 5.1 at baseline to 7.1 ± 4.4 12 months after therapy. Therapy in general was well tolerated and side effects related to rituximab were observed in 18% of patients [11]. A recent Chinese report compared rituximab versus CYC in refractory LN cases. Although the term "refractory" was not further defined and the previous CYC exposure was not stated, they found significantly higher response rates in the rituximab-treated patients (complete remission 64.7%, partial remission 19%). Moreover, a decline of anti-C1q antibodies to 11.9% from baseline was found in this study [37]. Of note, conflicting data exist regarding the value of anti-C1q antibodies in the assessment of renal involvement in SLE [38]. Rituximab ($4 \times 375\,mg/m^2$) in combination with two pulses CYC ($0.5\,g/m^2$, three weeks apart) improved overall renal function along with an overall response in proteinuria. Moreover, repeated renal biopsy indicated reduced tissue-based CD3, CD4 and CD20 staining after six months. Complete and partial renal remission could be achieved in three and one patient, whereas three patients had persistent albuminuria and hypoalbuminaemia (< 50% improvement) [12]. Addition of a single infusion of CYC with a fixed dose of 500 mg along with rituximab $375\,mg/m^2$ weekly four times led to a decline of proteinuria from 4.6 g at baseline to 0.45 g per day after 12 months [14]. A follow-on study including relapsing and refractory LN patients revealed a high response rate in patients with active glomerulonephritis (91%). Long term follow-up was available for 9 patients, in whom a reduction of proteinuria from 2.2 g at baseline to 0.5 g at 24 months was observed [13]. Results from the French AutoImmunity and Rituximab Registry revealed a response rate of 74% when rituximab was added to another immunosuppressive agent. Notably, 24% of patients with LN did not receive MMF or CYC before initiation of rituximab, hence these patients have not been classified as refractory cases [15]. Another French observational study reported response of 50% with a refractory disease course. However, two patients remained on haemodialysis at the time of last follow-up. Repeated renal biopsy revealed a decrease in the activity index in most cases [16]. In a large multi-centre survey of rituximab use in Spain a response rate of 82.5% (out of 63 patients) was reported. Although no concrete information about assessment of renal response was given, proteinuria decreased from 1.6 ± 2.4 g to 0.8 ± 1.2 g per day after a follow-up time of 6 ± 3 months. Infections and infusion-related side effects accounted for the majority of adverse events reported [17].

An Italian multi-centre study recruited 145 patients, of whom 68 had LN and were refractory following at least one immunosuppressive measure. Different schemes of rituximab administration were used. A stepwise reduction of proteinuria from 4.1 ± 2.9 to 1.1 ± 1.9 g/day was observed after 12 months. Overall remission rates were 94.1%, with 21 and 43 patients achieving complete and partial remission [39]. A more recent French study reported 17 CYC-resistant patients who received concomitant immunosuppression alongside rituximab. A response rate of 53% was reported (4 complete and 5 partial). However, even in patients with no response as defined by the authors, proteinuria decreased from 4 g/day to 1.32 g/day after 12 months. Among severe side effects, one patient presented with *Escherichia coli* pyelonephritis [40]. Japanese LN patients who were refractory to established therapy including high-dose corticosteroids and immunosuppressants were treated with different doses of rituximab (ranging from 1000 to 4000 mg). 30 out of 36 patients (83.3%) improved from BILAG A or B to BILAG C or D score at one year, accompanied by a decrease in serum creatinine and urinary protein-to-creatinine ratio [18] (see Table 2). A recent analysis of the British Isles Lupus Assessment Group Biologics Register revealed good efficacy and an acceptable safety profile of rituximab therapy in patients failing either MMF or CYC. No sub-analysis of patients with renal items ($n = 111$) scored on BILAG has been reported [41]. Despite the reported evidence of rituximab' efficacy in refractory disease, a recent case series showed that five out of seven patients had no improvement following rituximab which was accompanied by incomplete B-cell depletion [42]. This argues for examination of B-cell count following rituximab infusions and eventually administer additional rituximab in case of incomplete depletion.

APRIL (a proliferation-inducing ligand) and B-lymphocyte stimulator (BLyS), the latter also known as BAFF (B cell activating factor), are members of the tumour necrosis factor (TNF) family [43,44] and both are implicated in SLE pathogenesis potentially playing a role as therapeutic targets as well as putative biomarkers [45]. Belimumab, a fully humanised monoclonal antibody targeting BLyS/BAFF, has been licensed in the management of SLE (active LN and central nervous system lupus excluded), but real-life data support its use in selected cases with LN as well [46]. An increased baseline BLyS level was associated with

Table 2
Characteristics of patients with refractory LN treated with rituximab. Definition of refractory LN is highly diverse in different studies reported. * Adverse events were recorded in 28 patients of the total cohort (n = 42); *[1] adverse events were reported for the whole cohort of patients with refractory SLE; *[2] refractory and relapsing patients were combined in analyses; *[3] 10 patients did not receive either CYC or MMF before administration of rituximab; *[4] adverse events were given for the whole cohort comprising 136 patients who received rituximab therapy (non-refractory cases included); *[5] severe adverse events were given for the whole cohort; *[6] serious adverse events (grade 3 to 5) for all patients (n = 60) included in this study. Abbreviations: CRR = complete renal remission, HACA = human anti-chimeric antibodies, LON = late-onset neutropenia, PRES = posterior reversible encephalopathy syndrome, PRR = partial renal remission.

Country	Definition refractory LN	Number (patients)	Response rate (CRR/PRR)	Side effects
Mexico [7]	#1	13	76.8% (38.4%/38.4%)	LON (7.7%)
Mexico [8]	#1	22	54.5% (22.7%/31.8%)	Histoplasmosis (4.5%)
Colombia [9]	#1	32	64% (28%/36%)	39.3%*
Singapore [10]	#2	7	100% (42.9%/57.1%)	–
Korea [11]	#3	17	64.7% (0%/64.7%)	Infusion reaction (10.3%), infections (7.7%)*[1]
China [37]	Undefined	42	83.3% (64.3%/19%)	not reported
Sweden [12]	#4	7	57.1% (42.9%, 14.2%)	Neutropenic fever, infections (28.6%)
United Kingdom [14]	#5	6	100%	Serum sickness syndrome (9.1%), HACA production (9.1%)*[1]
United Kingdom [13]	#5	11*[2]	91% (36.4%, 54.5%)	Infusion reaction (45.2%), infections (25.8%), LON (3.2%)
France [15]	#6	32 (42)*	74% (45%, 29%)*[3]	Infusion reaction (16.2%), thromboembolic event (4.4%), severe infection (8.8%)*[4]
France [16]	#7	12	50% (25%/25%)	Infections (8.3%), LON (16.7%), PRES and cerebral haemorrhage (8.3%)
Spain [17]	#8	63	82.5%	38.9% (mainly infections and infusion reactions)*[1]
Italy [39]	#1	68	94.1% (30.9%/63.2%)	Severe adverse events (15/134)*[5]
France [40]	#6	17	53%	*Escherichia coli* pyelonephritis (5.9%)
Japan [18]	#9	36	83.3%	Brain haemorrhage (1.7%), cerebral infarction (1.7%), sepsis (1.7%), Infections (25%), neutropenia (1.7%), myocardial infarction (1.7%)*[6]

an early relapse (< 12 months) of disease. In general, a significant increase of BLyS levels was observed following rituximab therapy, whereas after 6–8 months, when B-cell repopulation was ongoing, BLyS levels decreased to baseline levels [47]. This finding suggests a rationale for a combined B-cell depletion and BLyS inhibition. This strategy has successfully been employed in several patients with refractory LN and may be a promising approach in refractory LN responding to rituximab with subsequent early relapse [48,49]. In addition to reduction of BLyS levels, combination of rituximab and belimumab diminished excessive neutrophil extracellular traps formation [50]. An interim-analysis of the CALIBRATE trial (NCT02260934) which either assigned patients to belimumab or placebo showed no clinical benefit of BLyS inhibition in the short term and longer follow-up data are warranted [51]. More trials combining rituximab with belimumab in the management of non-renal SLE are in progress (e.g., BEAT-LUPUS (ISRCTN47873003) and BLISS-BELIEVE (NCT03312907)).

During the last decade, several reports revealed efficacy of rituximab in patients with refractory LN and in terms of failure of a conventional immunosuppressive strategy, B-cell depletion might be considered as first choice given the response rates reported in its "real-life" use and the low number of serious adverse events (Table 2) [52]. In line with this suggestion is the high rate of complete or partial renal response in patients with refractory disease. However, class IV and class V LN and a mixed type on renal biopsy are more recalcitrant to B-cell depletion which has been shown in a recent meta-analysis [53] and addition of other immunosuppressive measures discussed below may be considered in patients with inadequate response. If rituximab is contraindicated due to previous severe infusion reaction or presence of human anti-chimeric antibodies, novel completely humanised CD20-depleting agents such as ofatumumab or obinutuzumab may be used in the treatment of refractory cases. The former has been successfully used in a patient with life-threatening refractory LN [54].

4.2. Calcineurin inhibitors – Tacrolimus and cyclosporine A

A recently published randomised controlled trial comparing tacrolimus (4 mg a day) and low-dose MMF (1 g a day) with CYC (6 pulses á 0.75 mg/m^2 with dose adjustments) revealed superior efficacy of "multi-target" therapy after 6 months in terms of response rates and complete renal remission. The difference observed was mainly attributable to a better response of difficult to treat class IV and V LN and mixed pattern (IV + V) on renal biopsy [55]. Another randomised controlled trial comparing tacrolimus (0.06–0.1 mg/kg a day) with MMF (2–3 g/d) showed non-inferiority of tacrolimus in induction of remission. Patients were switched to a maintenance treatment with azathioprine and a non-significant trend towards a higher relapse frequency was observed in the trial arm randomised to tacrolimus. During follow-up of 6 months, the change in renal function differed significantly between both groups with an increase of 14 ml/min in creatinine clearance observed in the MMF-arm and a stabilisation in the tacrolimus group [56]. Addition of a calcineurin inhibitor may be a reasonable option in addition to other immunosuppressive measures in the treatment of refractory class IV/V LN or mixed patterns.

In an earlier trial comparing "multi-target" therapy as described above (dosage adapted to trough levels) to CYC, a high percentage of patients received either CYC or MMF before. The rate of complete renal remission in intention-to-treat analysis was significantly higher (50% versus 5%) in the "multi-target" therapy arm, whereas partial response did not differ between groups. Serum creatinine normalised in all but one patient in each group, while the mean value of serum creatinine was similar [57]. In a Spanish single centre observational study, patients with MMF treatment were studied. In case of unresponsive disease or disease relapse despite MMF, tacrolimus (0.075 mg/kg/d) was added to the immunosuppressive regimen. 12 patients (70%) achieved a therapeutic response, of whom six had a complete and partial remission. Of note, all patients had either class IV or class V LN [58]. In a Chinese prospective observational study, tacrolimus (2 or 3 mg, depending on body weight) was added to the treatment in 26 CYC-resistant patients. Response (complete 38.5%, partial 50%) was observed in a majority of patients, which was accompanied by a mean decrease of proteinuria from 6.9 ± 4.5 g/d to 1.11 ± 1.1 g/d and a significant decline in SLEDAI. Interestingly, patients classified as non-responders had class III LN on biopsy [59]. Response of refractory class IV and V or combined IV/V was also observed in a small Korean study with a rate of

Table 3
Efficacy and side effects of calcineurin inhibitors in the treatment of refractory LN. Refractory LN was defined as: #1 refractory disease despite MMF therapy, #2 LN resistant to CYC treatment, #3 patients failed to respond to sufficient intravenous CYC therapy, #4 refractory to glucocorticoids (and other immunosuppressants), * Side effects are given for the whole cohort of patients (comprising a total of 70 MMF treated patients and tacrolimus was added in 17); *[1] No information regarding complete renal remission were given and side effects were reported for the whole cohort comprising 59 patients. Abbreviations used: CMV = cytomegalovirus, CRR = complete renal response, PRR = partial renal response.

Country	Definition refractory LN	Number (patients)	Response rate (CRR/PRR)	Side effects
China [57]	Not defined	20	90% (50%/40%)	Infections (20%), new onset hypertension (15%), leukopenia (10%), gastrointestinal symptoms (10%), new onset diabetes mellitus (5%)
Spain [58]	#6	17	70% (35%/35%)	Leucopenia (2.9%), gastrointestinal side effects (23%), tremor (1.4%)*
China [59]	#6	26	88.5% (38.5%/50%)	Aspergillosis/CMV (3.8%), new onset hypertension (3.8%), alopecia (3.8%)
Korea [60]	#4	9	78% (22%/56%)	Tremor (77.7%), new onset diabetes mellitus (11.1%)
USA [61]	#6	7	57.1% (14.3%/42.8%)	Infections (57.1%), diabetic ketoacidosis (14.3%)
Japan [62]	#5	26	61.5%*[1]	New onset hypertension (15.3%), renal dysfunction (11.9%)*[1]
Portugal [63]	#6	6	83.4% (66.7%/16.7%)	No adverse events

78%. Proteinuria decreased from a baseline UPCR of 2.19 to 0.44 g/g creatinine after 12 months. Despite these reassuring effects, the mean prednisolone dose remained above 10 mg/d at time of last follow-up [60]. In a small case series from a specialist centre in America including Caucasian and African American refractory LN patients, response was observed in four out of seven patients (one complete and three partial responses). However, severe side effects were observed leading to discontinuation of therapy in most patients [61]. In line with the observations of tacrolimus efficacy, cyclosporine A treatment led to good response rates in refractory LN. Combination of two treatment groups (concomitant stable or increased prednisolone dose) revealed a therapeutic response in 16/26 patients. Effects on proteinuria were observed as early as two weeks after initiation of therapy [62]. Six refractory cases with LN received cyclosporine A due to failure to achieve remission following MMF (2–3 g per day). Addition of cyclosporine A (2.6–3.7 mg/kg/day) led to a reduction of proteinuria from 2.4 g/24 h to 0.5 g/day. Four patients achieved complete remission, while one patient each had partial or no remission [63] (see Table 3).

Taken together, addition of tacrolimus or cyclosporine A to other immunosuppressive measures has been proven to be efficacious especially in patients with difficult to treat diffuse proliferative or membranous LN or a combination thereof, although there is the potential for reporting bias in these small retrospective series. Most of the evidence so far has been published in an Asian population and there is a strong need to prove this concept in other ethnicities. A novel calcineurin inhibitor, voclosporin, has recently shown efficacy over placebo in a phase II clinical trial, while serious adverse events were more frequent in the active treatment group [64]. This concept is currently tested in a phase III trial and may also be an option in those with refractory disease.

4.3. Extracorporeal treatment forms – New look on an old treatment strategy

Plasma exchange (PLEX) has been used intensively in combination with other immunosuppressive measures in the treatment of LN. However, enthusiasm was dampened following a negative randomised controlled trial conducted almost three decades ago. One limitation in the analysis of this data is the high cumulative dose of CYC which was administered orally and patients had mainly newly diagnosed LN. The study suggested no difference in both treatment arms [65]. A further study conducted by the Lupus Plasmapheresis Study Group was never published in full-text, although at least 87 patients have been recruited. One can only speculate that addition of PLEX to high dose steroids and per oral high dose CYC might lead to an abundance of severe complications [66]. Treatment-naïve LN, however, is rather responsive to immunosuppressive treatment and it is not clear if additional immunosuppression to standard of care increases renal response rates.

Addition of extracorporeal treatment measures have been shown to be efficacious either in the treatment of pregnant women with signs of active disease, antiphospholipid syndrome or in refractory LN. Immunoadsorption (IAS) has replaced PLEX in many countries, since the systemic effects are clearly favourable with potential implications on side effects, especially bleeding, anaphylactic complications or life-threatening infections [67–69], and removal of disease-specific antibodies with a rate outranging PLEX. Notably, high-affinity columns such as Ig-Therasorb® or Globaffin® have advantages in the removal of disease-specific antibodies as has been shown in a large observational study [70]. In their first report, Stummvoll and colleagues published their experience in the treatment of 16 patients with either refractory disease or contraindications towards standard treatment. Proteinuria decreased from 6.7 g/day at baseline to 2.9 g/d after 12 months. This renal response was accompanied by a decline of SLEDAI from 21 to 5 and of ECLAM from 7 to 3 during the same observational time. The steroid dosage could be reduced from 117 mg/day at baseline to 9 mg after 12 months. Anti-dsDNA antibodies fell from 391 IU/ml to 53 IU/ml after 12 months. From a side effect perspective, IAS was well tolerated with four episodes of severe infections recorded in two patients. Of these subjects, one died due to *Pseudomonas* septicaemia. However, this fatality may be related to concomitant CYC treatment rather than to IAS. Three anaphylactic reactions were observed, two were attributed to newly started intravenous drugs [70]. Eleven patients of their initial study entered a prolonged IAS programme. In those patients with no remission after one year ($n = 5$), proteinuria decreased significantly during prolonged follow-up from 4.3 ± 2.4 to 0.5 ± 0.4 g/day. During extended treatment, one patient had a disease flare, whereas in others disease has stabilised with a lower number of relapses compared to a comparator group receiving MMF (0.28 versus 0.89 per patient year, respectively). During prolonged IAS no more severe infectious complications were observed [71], further highlighting the influence of concomitant other measures such as high-dose steroids and cytotoxic agents on infectious risk.

In conclusion, extracorporeal treatment is a reasonable option in patients with a refractory disease course or in whom a more aggressive treatment regimen is contraindicated (i.e., with concomitant severe infectious complications). Given the low frequency of severe side effects observed during and following IAS, this technique may be superior to PLEX. The latter can be employed in centres where IAS is not available, although both randomised trials (one unpublished) did not support this suggestion [72]. However, one small multi-centre trial added either PLEX or cytotoxic drugs (azathioprine or CYC) when patients had no response following three weeks of steroid therapy. There was a comparable response, however the number of patients was small and does not allow any definite conclusions. We emphasise that a recruitment bias may be responsible for the results of the published randomised controlled trial with a negative result [73], since newly diagnosed patients were recruited along with relapsing/refractory disease and more recent case reports and series have highlighted efficacy of PLEX in

difficult to treat LN.

4.4. Stem cell transplantation – From autologous to umbilical cord mesenchymal stem cell transplantation

In patients with refractory SLE and LN, autologous stem cell transplantation has led to good control of active disease but with relapses in 50% by three years and a level of toxicity and treatment related mortality that has been proved unattractive to further trials or routine use. Results from a multi-centre survey of the European Group for Blood and Marrow Transplantation (EBMT) and EULAR registry with inclusion of predominant LN or other disease manifestations revealed a remission rate (defined as SLEDAI < 3) of 66% by six months, whereas 32% had a relapse in the subsequent follow-up and 12 fatalities occurred, of which 7 were attributed to the procedure. Given the high rate of post-transplant immunosuppression prescription (70% of patients) this procedure seems discouraging [74]. In a follow-up study, a report on 28 patients again with a majority having renal involvement indicated a disease-free survival of 55% for 2 years, with a relapse incidence of 56 ± 11% and five fatalities including three due to infections, one each due to secondary autoimmune phenomenon and progressive SLE [75]. A large single centre report from the United States revealed a low rate of procedure-related mortality, along with a 50% probability of disease free survival after 5 years. Autologous stem cell transplantation was employed due to renal disease in 20% of patients, whereas half of the patients had evidence of LN in the past [76]. A follow-up study implementing two different non-myeloablative regimens, namely CYC (200 mg/kg) and alemtuzumab (60 mg) or CYC (200 mg/kg), rATG (thymoglobulin) (5.5 mg/kg) and rituximab (1 g), was performed in the same centre. None of the four patients receiving the former regimen attained remission, while remission was achieved in 92% at 6 months with a long-term remission rate of 62% at 5 years post stem cell transplantation. Notably, LN was the manifestation leading to transplantation in 11/30 subjects. No treatment related fatalities were observed despite a large number of co-morbidities in a significant number of participants [77].

Alternatively, allogenic transplantation of mesenchymal stem or stromal cells (MSC) has been employed. MSCs possess immunomodulatory functions, including their ability to stimulate differentiation and proliferation of regulatory T cells [78]. MSC transplantation was performed in 15 patients with refractory LN. After 12 months of follow-up proteinuria decreased from 2505.0 ± 1323.9 at baseline to 858.0 ± 800.7 mg/day. In line with this significant improvement, SLEDAI decreased from 12.2 ± 3.3 to 3.2 ± 2.8 in the same observational period and two renal relapses were observed. Reassuringly, no life-threatening side effects following the procedure could be observed [79]. A follow-up study from the same group investigated the role of allogenic bone marrow and/or umbilical cord mesenchymal stem/stromal cell (MSC) transplantation in 81 patients with refractory LN. Notably, remission was achieved in 60.5% of patients, along with a significant reduction of BILAG and SLEDAI scores in this cohort. Proteinuria decreased from 2.74 ± 1.2 to 1.52 ± 1.04 g/d and GFR improved from 58.55 ± 19.16 to 69.51 ± 27.93 ml/min. Relapse was recorded in 22.4% of the patients and 4 died during follow-up. However, fatalities were judged to be unrelated to the procedure [80]. Long term follow-up of five years revealed that 13 patients died, while of the remainders 28 (out of 68) were in complete (22) or partial (6) remission [81]. In another study umbilical cord MSC transplantation was chosen to treat mainly refractory LN. A decline of proteinuria reaching significant changes was observed after 3 months and in patients with longer follow-up after 6 months, along with an improvement of renal function in those with increased creatinine at baseline. Again no treatment-related side effects were observed during follow-up [82]. A subsequent multi-centre trial including a majority of patients with LN indicated a major clinical response and a partial clinical response in 27.5 and 32.5% of patients, respectively. The overall survival rate during the follow-up time of 12 months was 92.5% with fatalities unrelated to the procedure as judged by the investigators. Proteinuria decreased from 2.24 ± 1.43 g at baseline to 1.41 ± 1.33 g after 12 months and serum creatinine stabilised during follow-up [83]. Results of a randomised controlled trial dampened enthusiasm, since it was stopped after enrolment of 18 patients. Remission rates were comparable between patients undergoing MSC (75%) and those assigned into the placebo group (83%). Moreover, one patient died due to severe pneumonia in the MSC group [84].

In conclusion, stem cell transplantation as reported in the EBMT/EULAR registry was mainly used when damage accrual was already present. This may explain the high procedure-related mortality and due to a severe disease course the high rate of relapse following autologous stem cell transplantation. In contrast, single centre results from the United States and emerging strategies such as mesenchymal and umbilical cord mesenchymal stem cell transplantation indicated a low rate of procedure-related fatalities, since patients underwent transplantation early in their disease course and overall a good renal outcome was proposed. Nevertheless, we believe that alternative strategies as described above are more encouraging since renal response indicated similar remission and relapse rates along with a reduction of severe side effects compared to stem cell transplantation and this procedure should be confined to selected cases [85].

4.5. Alternative immunosuppressives

In a Chinese series, patients with either refractory disease or contraindication towards CYC treatment, leflunomide with an initial dosage of 100 mg (for 3 days) followed by 20 mg subsequently for 52 weeks showed efficacy in 76% of patients with an overall reduction of proteinuria from 3.5 to 1.7 g/day [86]. After high-dose immunoablative CYC (50 mg/kg body weight for 4 consecutive days, accompanied by *Pneumocystis jirovecii* prophylaxis) four patients had a complete response, whereas three patients showed a partial response and two failed induction treatment. In the latter group one patient progressed to end stage renal failure. Reassuringly, no patient presented a renal relapse during follow-up [87]. Mizoribine, an immunosuppressant inhibiting inosine monophosphate dehydrogenase, was employed in a Japanese series of 17 patients with resistant LN. A decline in urinary protein excretion from 194 ± 208 to 114 ± 106 mg/dl after 24 months could be observed [88]. In seven patients with LN with CYC failure, addition of high dose intravenous immunoglobulin (1–6 courses of 400 mg/kg over 5 consecutive days) yielded a significant decline in proteinuria after 6 months which was accompanied by an improvement in serum albumin and a reduction in serum cholesterol [89]. Others have shown that high-dose intravenous azathioprine along with per oral azathioprine during the intervals as well as intravenous methotrexate in combination with pulse CYC may be an alternative in difficult to treat LN refractory to standard immunosuppressive measures [90,91]. Thalidomide, which has shown efficacy in cutaneous SLE, has been successfully used in two patients with refractory LN. Mild peripheral neuropathy was noted in one case [92].

Bortezomib, a proteasome inhibitor, was tested in 12 patients with refractory SLE, of whom eight had renal involvement. Overall, a significant reduction of disease activity as measured by SLEDAI was achieved. Proteinuria decreased from 2221 to 867 mg/day during the follow-up period. Severe adverse events resulting in hospitalisation were reported in four patients [93]. Efficacy of a bortezomib-based regimen was efficacious in a cohort of Chinese patients with either a refractory or relapsing disease course [94]. Bortezomib-induced a rapid depletion of plasma cells (PC), but the regeneration was fast. This was in part explained by an approximately 2-fold increase in BLyS at the end of treatment. Combination therapy with rituximab was proposed, but belimumab may be an alternative strategy in this setting which has been successfully demonstrated in two cases [95,96].

5. Conclusion

The treat-to-target initiative in SLE recommended that prevention of damage accrual is a major therapeutic goal, since damage leads to morbidity and is associated with mortality, especially in patients with SLE and end stage renal disease [97,98]. Improving the health related quality of life is one important outcome and strategic approaches to target therapies need to be employed [99]. Moreover, our treatment target should be remission and when remission is not achievable the lowest possible disease activity measure by validated disease activity scores should be reached [98]. To achieve such goals in refractory disease, a change in the treatment strategy has to be considered rather early (3–4 months after initiation of therapy) to prevent irreversible kidney damage. In order to further highlight the importance of refractoriness in SLE, a clear definition of refractory LN is desired, since comparability of different observational studies reporting on outcome following treatment is limited given the fact of diverse conceptions of "refractory". This may be addressed by a follow-on initiative of the treat-to-target SLE with the aim to improve patient care in this cohort of high-risk patients.

The armamentarium of treating refractory LN has been extended over the last decade. The recommendation of the joint publication of the EULAR/ERA-EDTA suggested a switch from either MMF to CYC or vice versa in terms of inefficacy or treatment related side effects or in a next instance rituximab should be added [5]. Rituximab has shown encouraging results in the treatment of refractory LN, especially in class III and IV LN and to a lower extent in mixed classes and membranous LN [53]. Since experience, however, was published all over the world we recommend rituximab as first option in patients with a refractory disease course. In contrast, calcineurin inhibitors have been mainly tested in Japan and China in these indications. The results published so far have highlighted a good efficacy of tacrolimus especially in difficult to treat LN classes IV and V. Howsoever, although results in treatment-naïve patients are accumulating, more results including other ethnicities are clearly warranted. Since procedure-related side effects are rarely seen in patients undergoing IAS, we think this technique is elegant and yielded good efficacy in patients with refractory LN or in those with contraindication towards standard therapy. Since evidence is limited to one larger case series [70], a clinical trial comparing the efficacy of IAS in combination with standard of care to standard of care alone is required. Stem cell transplantation in the course of refractory cases has attracted attention in the last two decades. Since the introduction of novel and efficacious medical therapies, the interest is slightly decreasing. Noteworthy, studies from China revealed efficacy of mesenchymal and umbilical cord mesenchymal stem cell transplantation, which led to a low procedure-related fatality rate. In patients with a high cumulative organ damage, mortality rates related either to disease or procedure are high and have to be taken into account when counselling for such an approach. Other strategies employed so far have been reported in small cohorts, but especially intravenous immunoglobulins may have a role in the treatment of refractory LN cases. Emerging novel immunosuppressive measures will further increase our treatment options in LN and in cases with refractory disease course.

Adjunct therapy should be optimised in the context of refractory LN and non-adherence to the prescribed medication should be ruled out. In line with the EULAR/ERA-EDTA recommendations [5], antimalarials (hydroxychloroquine or chloroquine) should be commenced if contraindications are ruled out, given their effects on production of interferon-α and tumour necrosis factor-α [100], ability to decrease further TH17-related cytokines [101] and more strikingly the association between interferon-α decrease and disease activity reduction [102]. Moreover, all patients with renal involvement should receive ACE-inhibition or in terms of intolerance angiotensin receptor blockers, especially when blood pressure is elevated. Notably, addition of ACE inhibition to the treatment of SLE may prevent onset of LN as has been shown in a multi-ethnic US cohort [6]. In order to prevent thromboembolic events anticoagulation may be considered when serum albumin is below 20 g/l, especially when patients have an underlying antiphospholipid syndrome. Based on the high rate of premature atherosclerosis, lowering LDL-cholesterol to a value below 100 mg/dl was suggested by the recommendation of the EULAR/ERA-EDTA. However, clear evidence regarding the latter recommendation is lacking [5].

Conflict of interest

A.K. has been supported by the ERA-EDTA with a long-term fellowship (12 months) from August 2014 to August 2015 and has received speaking fees from TerumoBCT and Miltenyi Biotech. B.B. has received a fellowship grant from Addenbrooke's Charitable Trust and Cambridge Biomedical research Centre. L.F.Q. has been supported by the Spanish Society of Nephrology (SENEFRO) and the committee of medical delegates-professional association Hospital Clinic de Barcelona. D.R.W.J. has received research grants and consulting fees from Roche/Genentech and is supported by the Cambridge Biomedical Research Centre.

Author contributions

AK, BB, and DRWJ designed the study, AK and BB coordinated data acquisition and drafted the manuscript. All authors participated in critical revision of the manuscript and read and approved the final version of the manuscript.

References

[1] Rahman A, Isenberg DA. Systemic lupus erythematosus. N Engl J Med 2008;358:929–39.
[2] Cervera R, Khamashta MA, Font J, Sebastiani GD, Gil A, Lavilla P, et al. Systemic lupus erythematosus: clinical and immunologic patterns of disease expression in a cohort of 1,000 patients. The European Working Party on Systemic Lupus Erythematosus. Medicine (Baltimore) 1993;72:113–24.
[3] Hahn BH, McMahon MA, Wilkinson A, Wallace WD, Daikh DI, Fitzgerald JD, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res (Hoboken) 2012;64:797–808.
[4] Christopher-Stine L, Siedner M, Lin J, Haas M, Parekh H, Petri M, et al. Renal biopsy in lupus patients with low levels of proteinuria. J Rheumatol 2007;34:332–5.
[5] Bertsias GK, Tektonidou M, Amoura Z, Aringer M, Bajema I, Berden JH, 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;71:1771–82.
[6] Duran-Barragan S, McGwin Jr. G, Vila LM, Reveille JD, Alarcon GS, LUMINA (LIX): a multiethnic US cohort. Angiotensin-converting enzyme inhibitors delay the occurrence of renal involvement and are associated with a decreased risk of disease activity in patients with systemic lupus erythematosus–results from LUMINA (LIX): a multiethnic US cohort. Rheumatology (Oxford) 2008;47:1093–6.
[7] Garcia-Carrasco M, Mendoza-Pinto C, Sandoval-Cruz M, Soto-Vega E, Beltran-Castillo A, Jimenez-Hernandez M, et al. Anti-CD20 therapy in patients with refractory systemic lupus erythematosus: a longitudinal analysis of 52 Hispanic patients. Lupus 2010;19:213–9.
[8] Vigna-Perez M, Hernandez-Castro B, Paredes-Saharopulos O, Portales-Perez D, Baranda L, Abud-Mendoza C, et al. Clinical and immunological effects of rituximab in patients with lupus nephritis refractory to conventional therapy: a pilot study. Arthritis Res Ther 2006;8:R83.
[9] Pinto LF, Velasquez CJ, Prieto C, Mestra L, Forero E, Marquez JD. Rituximab induces a rapid and sustained remission in Colombian patients with severe and refractory systemic lupus erythematosus. Lupus 2011;20:1219–26.
[10] Lateef A, Lahiri M, Teng GG, Vasoo S. Use of rituximab in the treatment of refractory systemic lupus erythematosus: Singapore experience. Lupus 2010;19:765–70.
[11] Bang SY, Lee CK, Kang YM, Kim HA, Suh CH, Chung WT, et al. Multicenter retrospective analysis of the effectiveness and safety of rituximab in korean patients with refractory systemic lupus erythematosus. Autoimmune Dis 2012;2012:565039.
[12] Gunnarsson I, Sundelin B, Jonsdottir T, Jacobson SH, Henriksson EW, van Vollenhoven RF. Histopathologic and clinical outcome of rituximab treatment in patients with cyclophosphamide-resistant proliferative lupus nephritis. Arthritis Rheum 2007;56:1263–72.
[13] Catapano F, Chaudhry AN, Jones RB, Smith KG, Jayne DW. Long-term efficacy and safety of rituximab in refractory and relapsing systemic lupus erythematosus.

Nephrol Dial Transplant 2010;25:3586–92.
[14] Smith KG, Jones RB, Burns SM, Jayne DR. Long-term comparison of rituximab treatment for refractory systemic lupus erythematosus and vasculitis: remission, relapse, and re-treatment. Arthritis Rheum 2006;54:2970–82.
[15] Terrier B, Amoura Z, Ravaud P, Hachulla E, Jouenne R, Combe B, 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;62:2458–66.
[16] Melander C, Sallee M, Trolliet P, Candon S, Belenfant X, Daugas E, et al. Rituximab in severe lupus nephritis: early B-cell depletion affects long-term renal outcome. Clin J Am Soc Nephrol 2009;4:579–87.
[17] Fernandez-Nebro A, de la Fuente JL, Carreno L, Izquierdo MG, Tomero E, Rua-Figueroa I, et al. Multicenter longitudinal study of B-lymphocyte depletion in refractory systemic lupus erythematosus: the LESIMAB study. Lupus 2012;21:1063–76.
[18] Iwata S, Saito K, Hirata S, Ohkubo N, Nakayamada S, Nakano K, et al. Efficacy and safety of anti-CD20 antibody rituximab for patients with refractory systemic lupus erythematosus. Lupus 2018;27:802–11.
[19] KDIGO. Clinical Practice Guideline for Glomerulonephritis. 2012http://www.kdigo.org/clinical_practice_guidelines/pdf/KDIGO-GN-Guideline.pdf.
[20] Wilhelmus S, Bajema IM, Bertsias GK, Boumpas DT, Gordon C, Lightstone L, et al. Lupus nephritis management guidelines compared. Nephrol Dial Transplant 2016;31:904–13.
[21] Houssiau FA, Vasconcelos C, D'Cruz D, Sebastiani GD, de Ramon Garrido E, Danieli MG, et al. Early response to immunosuppressive therapy predicts good renal outcome in lupus nephritis: lessons from long-term followup of patients in the euro-lupus nephritis trial. Arthritis Rheum 2004;50:3934–40.
[22] Reich HN, Gladman DD, Urowitz MB, Bargman JM, Hladunewich MA, Lou W, et al. Persistent proteinuria and dyslipidemia increase the risk of progressive chronic kidney disease in lupus erythematosus. Kidney Int 2011;79:914–20.
[23] Isenberg D, Appel GB, Contreras G, Dooley MA, Ginzler EM, Jayne D, et al. Influence of race/ethnicity on response to lupus nephritis treatment: the ALMS study. Rheumatology (Oxford) 2010;49:128–40.
[24] Alsuwaida A, Husain S, Alghonaim M, AlOudah N, Alwakeel J, Ullah A, et al. Strategy for second kidney biopsy in patients with lupus nephritis. Nephrol Dial Transplant 2012;27:1472–8.
[25] Zickert A, Sundelin B, Svenungsson E, Gunnarsson I. Role of early repeated renal biopsies in lupus nephritis. Lupus Sci Med 2014;1:e000018.
[26] Karim MY, Alba P, Cuadrado MJ, Abbs IC, D'Cruz DP, Khamashta MA, et al. Mycophenolate mofetil for systemic lupus erythematosus refractory to other immunosuppressive agents. Rheumatology (Oxford) 2002;41:876–82.
[27] Diaz-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;11:357–64.
[28] Ward MM, Sundaramurthy S, Lotstein D, Bush TM, Neuwelt CM, Street Jr. RL. Participatory patient-physician communication and morbidity in patients with systemic lupus erythematosus. Arthritis Rheum 2003;49:810–8.
[29] Petri M, Perez-Gutthann S, Longenecker JC, Hochberg M. Morbidity of systemic lupus erythematosus: role of race and socioeconomic status. Am J Med 1991;91:345–53.
[30] Frances C, Cosnes A, Duhaut P, Zahr N, Soutou B, Ingen-Housz-Oro S, et al. Low blood concentration of hydroxychloroquine in patients with refractory cutaneous lupus erythematosus: a French multicenter prospective study. Arch Dermatol 2012;148:479–84.
[31] Jones RB, Walsh M, Chaudhry AN, Smith KG, Jayne DR. Randomized trial of enteric-coated mycophenolate sodium versus mycophenolate mofetil in multi-system autoimmune disease. Clin Kidney J 2014;7:562–8.
[32] Houssiau FA, Vasconcelos C, D'Cruz D, Sebastiani GD, Garrido Ed Ede R, Danieli MG, et al. Immunosuppressive therapy in lupus nephritis: the Euro-Lupus Nephritis Trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. Arthritis Rheum 2002;46:2121–31.
[33] Zeher M, Doria A, Lan J, Aroca G, Jayne D, Boletis I, et al. Efficacy and safety of enteric-coated mycophenolate sodium in combination with two glucocorticoid regimens for the treatment of active lupus nephritis. Lupus 2011;20:1484–93.
[34] Rivera F, Merida E, Illescas ML, Lopez-Rubio E, Frutos MA, Garcia-Frias P, et al. Mycophenolate in refractory and relapsing lupus nephritis. Am J Nephrol 2014;40:105–12.
[35] Appel GB, Contreras G, Dooley MA, Ginzler EM, Isenberg D, Jayne D, et al. Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. J Am Soc Nephrol 2009;20:1103–12.
[36] 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;64:1215–26.
[37] Zhang J, Zhao Z, Hu X. Effect of rituximab on serum levels of anti-C1q and Antineutrophil cytoplasmic autoantibodies in refractory severe lupus nephritis. Cell Biochem Biophys 2015;72:197–201.
[38] Kronbichler A, Mayer G. Renal involvement in autoimmune connective tissue diseases. BMC Med 2013;11:95.
[39] Iaccarino L, Bartoloni E, Carli L, Ceccarelli F, Conti F, De Vita S, et al. Efficacy and safety of off-label use of rituximab in refractory lupus: data from the Italian multicentre Registry. Clin Exp Rheumatol 2015;33:449–56.
[40] Contis A, Vanquaethem H, Truchetet ME, Couzi L, Rigothier C, Richez C, et al. Analysis of the effectiveness and safety of rituximab in patients with refractory lupus nephritis: a chart review. Clin Rheumatol 2016;35:517–22.
[41] McCarthy EM, Sutton E, Nesbit S, White J, Parker B, Jayne D, et al. Short-term efficacy and safety of rituximab therapy in refractory systemic lupus erythematosus: results from the British Isles Lupus Assessment Group Biologics Register. Rheumatology (Oxford) 2018;57:470–9.
[42] Manou-Stathopoulou S, Robson MG. Risk of clinical deterioration in patients with lupus nephritis receiving rituximab. Lupus 2016;25:1299–306.
[43] Hahne M, Kataoka T, Schroter M, Hofmann K, Irmler M, Bodmer JL, et al. APRIL, a new ligand of the tumor necrosis factor family, stimulates tumor cell growth. J Exp Med 1998;188:1185–90.
[44] Schneider P, MacKay F, Steiner V, Hofmann K, Bodmer JL, Holler N, et al. BAFF, a novel ligand of the tumor necrosis factor family, stimulates B cell growth. J Exp Med 1999;189:1747–56.
[45] Samy E, Wax S, Huard B, Hess H, Schneider P. Targeting BAFF and APRIL in systemic lupus erythematosus and other antibody-associated diseases. Int Rev Immunol 2017;36:3–19.
[46] Marcondes F, Scheinberg M. Belimumab in the treatment of systemic lupus erythematous: an evidence based review of its place in therapy. Autoimmun Rev 2018;17:103–7.
[47] Cambridge G, Isenberg DA, Edwards JC, Leandro MJ, Migone TS, Teodorescu M, et al. B cell depletion therapy in systemic lupus erythematosus: relationships among serum B lymphocyte stimulator levels, autoantibody profile and clinical response. Ann Rheum Dis 2008;67:1011–6.
[48] Kraaij T, Huizinga TW, Rabelink TJ, Teng YK. Belimumab after rituximab as maintenance therapy in lupus nephritis. Rheumatology (Oxford) 2014;53:2122–4.
[49] Gualtierotti R, Borghi MO, Gerosa M, Schioppo T, Larghi P, Geginat J, et al. Successful sequential therapy with rituximab and belimumab in patients with active systemic lupus erythematosus: a case series. Clin Exp Rheumatol 2018;36:643–7.
[50] Kraaij T, Kamerling SWA, de Rooij ENM, van Daele PLA, Bredewold OW, Bakker JA, et al. The NET-effect of combining rituximab with belimumab in severe systemic lupus erythematosus. J Autoimmun 2018;91:45–54.
[51] McClure M, Gopaluni S, Jayne D, Jones R. B cell therapy in ANCA-associated vasculitis: current and emerging treatment options. Nat Rev Rheumatol 2018;14:580–91.
[52] Kronbichler A, Windpessl M, Pieringer H, Jayne DRW. Rituximab for immunologic renal disease: what the nephrologist needs to know. Autoimmun Rev 2017;16:633–43.
[53] Weidenbusch M, Rommele C, Schrottle A, Anders HJ. Beyond the LUNAR trial. Efficacy of rituximab in refractory lupus nephritis. Nephrol Dial Transplant 2013;28:106–11.
[54] Thornton CC, Ambrose N, Ioannou Y. Ofatumumab: a novel treatment for severe systemic lupus erythematosus. Rheumatology (Oxford) 2015;54:559–60.
[55] Liu Z, Zhang H, Liu Z, Xing C, Fu P, Ni Z, et al. Multitarget therapy for induction treatment of lupus nephritis: a randomized trial. Ann Intern Med 2015;162:18–26.
[56] Mok CC, Ying KY, Yim CW, Siu YP, Tong KH, C.H. To, et al. Tacrolimus versus mycophenolate mofetil for induction therapy of lupus nephritis: a randomised controlled trial and long-term follow-up. Ann Rheum Dis 2016;75:30–6.
[57] Bao H, Liu ZH, Xie HL, Hu WX, Zhang HT, Li LS. Successful treatment of class V +IV lupus nephritis with multitarget therapy. J Am Soc Nephrol 2008;19:2001–10.
[58] Cortes-Hernandez J, Torres-Salido MT, Medrano AS, Tarres MV, Ordi-Ros J. Long-term outcomes–mycophenolate mofetil treatment for lupus nephritis with addition of tacrolimus for resistant cases. Nephrol Dial Transplant 2010;25:3939–48.
[59] Fei Y, Wu Q, Zhang W, Chen H, Hou Y, Xu D, et al. Low-dose tacrolimus in treating lupus nephritis refractory to cyclophosphamide: a prospective cohort study. Clin Exp Rheumatol 2013;31:62–8.
[60] Lee T, Oh KH, Joo KW, Kim YS, Ahn C, Han JS, et al. Tacrolimus is an alternative therapeutic option for the treatment of refractory lupus nephritis. Lupus 2010;19:974–80.
[61] Lanata CM, Mahmood T, Fine DM, Petri M. Combination therapy of mycophenolate mofetil and tacrolimus in lupus nephritis. Lupus 2010;19:935–40.
[62] Ogawa H, Kameda H, Amano K, Takeuchi T. Efficacy and safety of cyclosporine a in patients with refractory systemic lupus erythematosus in a daily clinical practice. Lupus 2010;19:162–9.
[63] Jesus D, Rodrigues M, da Silva JAP, Ines L. Multitarget therapy of mycophenolate mofetil and cyclosporine a for induction treatment of refractory lupus nephritis. Lupus 2018;27:1358–62.
[64] Rovin BH, Solomons N, Pendergraft 3rd WF, Dooley MA, Tumlin J, Romero-Diaz J, et al. A randomized, controlled double-blind study comparing the efficacy and safety of dose-ranging voclosporin with placebo in achieving remission in patients with active lupus nephritis. Kidney Int 2019;95:219–31.
[65] Lewis EJ, Hunsicker LG, Lan SP, Rohde RD, Lachin JM. A controlled trial of plasmapheresis therapy in severe lupus nephritis. The lupus nephritis collaborative study group. N Engl J Med 1992;326:1373–9.
[66] Euler HH, Guillevin L. Plasmapheresis and subsequent pulse cyclophosphamide in severe systemic lupus erythematosus. An interim report of the lupus Plasmapheresis study group. Ann Med Interne (Paris) 1994;145:296–302.
[67] Aringer M, Smolen JS, Graninger WB. Severe infections in plasmapheresis-treated systemic lupus erythematosus. Arthritis Rheum 1998;41:414–20.
[68] Euler HH, Schroeder JO, Harten P, Zeuner RA, Gutschmidt HJ. Treatment-free remission in severe systemic lupus erythematosus following synchronization of plasmapheresis with subsequent pulse cyclophosphamide. Arthritis Rheum 1994;37:1784–94.
[69] Zollner S, Pablik E, Druml W, Derfler K, Rees A, Biesenbach P. Fibrinogen reduction and bleeding complications in plasma exchange, immunoadsorption and a combination of the two. Blood Purif 2014;38:160–6.
[70] Stummvoll GH, Aringer M, Smolen JS, Schmaldienst S, Jimenez-Boj E, Horl WH,

et al. IgG immunoadsorption reduces systemic lupus erythematosus activity and proteinuria: a long term observational study. Ann Rheum Dis 2005;64:1015–21.
[71] Stummvoll GH, Schmaldienst S, Smolen JS, Derfler K, Biesenbach P. Lupus nephritis: prolonged immunoadsorption (IAS) reduces proteinuria and stabilizes global disease activity. Nephrol Dial Transplant 2012;27:618–26.
[72] Kronbichler A, Brezina B, Quintana LF, Jayne DR. Efficacy of plasma exchange and immunoadsorption in systemic lupus erythematosus and antiphospholipid syndrome: a systematic review. Autoimmun Rev 2016;15:38–49.
[73] Wallace DJ. Plasmapheresis for lupus nephritis. N Engl J Med 1992;327:1029. [author reply 1029-30].
[74] Jayne D, Passweg J, Marmont A, Farge D, Zhao X, Arnold R, et al. Autologous stem cell transplantation for systemic lupus erythematosus. Lupus 2004;13:168–76.
[75] Alchi B, Jayne D, Labopin M, Demin A, Sergeevicheva V, Alexander T, et al. Autologous haematopoietic stem cell transplantation for systemic lupus erythematosus: data from the European Group for Blood and Marrow Transplantation registry. Lupus 2013;22:245–53.
[76] Burt RK, Traynor A, Statkute L, Barr WG, Rosa R, Schroeder J, et al. Nonmyeloablative hematopoietic stem cell transplantation for systemic lupus erythematosus. JAMA 2006;295:527–35.
[77] Burt RK, Han X, Gozdziak P, Yaung K, Morgan A, Clendenan AM, et al. Five year follow-up after autologous peripheral blood hematopoietic stem cell transplantation for refractory, chronic, corticosteroid-dependent systemic lupus erythematosus: effect of conditioning regimen on outcome. Bone Marrow Transplant 2018;53:692–700.
[78] Mosanya CH, Isaacs JD. Tolerising cellular therapies: what is their promise for autoimmune disease? Ann Rheum Dis 2018;78(3):297–310.
[79] Liang J, Zhang H, Hua B, Wang H, Lu L, Shi S, et al. Allogenic mesenchymal stem cells transplantation in refractory systemic lupus erythematosus: a pilot clinical study. Ann Rheum Dis 2010;69:1423–9.
[80] Gu F, Wang D, Zhang H, Feng X, Gilkeson GS, Shi S, et al. Allogeneic mesenchymal stem cell transplantation for lupus nephritis patients refractory to conventional therapy. Clin Rheumatol 2014;33:1611–9.
[81] Wang D, Zhang H, Liang J, Wang H, Hua B, Feng X, et al. A long-term follow-up study of allogeneic Mesenchymal stem/stromal cell transplantation in patients with drug-resistant systemic lupus Erythematosus. Stem Cell Reports 2018;10:933–41.
[82] Sun L, Wang D, Liang J, Zhang H, Feng X, Wang H, et al. Umbilical cord mesenchymal stem cell transplantation in severe and refractory systemic lupus erythematosus. Arthritis Rheum 2010;62:2467–75.
[83] Wang D, Li J, Zhang Y, Zhang M, Chen J, Li X, et al. Umbilical cord mesenchymal stem cell transplantation in active and refractory systemic lupus erythematosus: a multicenter clinical study. Arthritis Res Ther 2014;16:R79.
[84] Deng D, Zhang P, Guo Y, Lim TO. A randomised double-blind, placebo-controlled trial of allogeneic umbilical cord-derived mesenchymal stem cell for lupus nephritis. Ann Rheum Dis 2017;76:1436–9.
[85] Leone A, Radin M, Almarzooqi AM, Al-Saleh J, Roccatello D, Sciascia S, et al. Autologous hematopoietic stem cell transplantation in systemic lupus Erythematosus and antiphospholipid syndrome: a systematic review. Autoimmun Rev 2017;16:469–77.
[86] Tam LS, Li EK, Wong CK, Lam CW, Li WC, Szeto CC. Safety and efficacy of leflunomide in the treatment of lupus nephritis refractory or intolerant to traditional immunosuppressive therapy: an open label trial. Ann Rheum Dis 2006;65:417–8.
[87] Petri M, Jones RJ, Brodsky RA. High-dose cyclophosphamide without stem cell transplantation in systemic lupus erythematosus. Arthritis Rheum 2003;48:166–73.
[88] Nishi E, Kameda H, Ogawa H, Nagasawa H, Takei H, Okuyama A, et al. Efficacy of weekly mizoribine pulse therapy in refractory lupus nephritis. Mod Rheumatol 2013;23:97–103.
[89] Levy Y, Sherer Y, George J, Rovensky J, Lukac J, Rauova L, et al. Intravenous immunoglobulin treatment of lupus nephritis. Semin Arthritis Rheum 2000;29:321–7.
[90] Benenson E, Fries JW, Heilig B, Pollok M, Rubbert A. High-dose azathioprine pulse therapy as a new treatment option in patients with active Wegener's granulomatosis and lupus nephritis refractory or intolerant to cyclophosphamide. Clin Rheumatol 2005;24:251–7.
[91] Lehman TJ, Edelheit BS, Onel KB. Combined intravenous methotrexate and cyclophosphamide for refractory childhood lupus nephritis. Ann Rheum Dis 2004;63:321–3.
[92] Raturi R, Patel AA, Carter JD. Two cases demonstrating thalidomide's efficacy in refractory lupus nephritis. Clin Rheumatol 2017;36:725–8.
[93] Alexander T, Sarfert R, Klotsche J, Kuhl AA, Rubbert-Roth A, Lorenz HM, et al. The proteasome inhibitior bortezomib depletes plasma cells and ameliorates clinical manifestations of refractory systemic lupus erythematosus. Ann Rheum Dis 2015;74:1474–8.
[94] Zhang H, Liu Z, Huang L, Hou J, Zhou M, Huang X, et al. The short-term efficacy of bortezomib combined with glucocorticoids for the treatment of refractory lupus nephritis. Lupus 2017;26:952–8.
[95] Alexander T, Cheng Q, Klotsche J, Khodadadi L, Waka A, Biesen R, et al. Proteasome inhibition with bortezomib induces a therapeutically relevant depletion of plasma cells in SLE but does not target their precursors. Eur J Immunol 2018;48:1573–9.
[96] Sjowall C, Hjorth M, Eriksson P. Successful treatment of refractory systemic lupus erythematosus using proteasome inhibitor bortezomib followed by belimumab: description of two cases. Lupus 2017;26:1333–8.
[97] Cervera R, Khamashta MA, Font J, Sebastiani GD, Gil A, Lavilla P, et al. Morbidity and mortality in systemic lupus erythematosus during a 10-year period: a comparison of early and late manifestations in a cohort of 1,000 patients. Medicine (Baltimore) 2003;82:299–308.
[98] Hambardzumyan K, Bolce R, Saevarsdottir S, Cruickshank SE, Sasso EH, Chernoff D, et al. Pretreatment multi-biomarker disease activity score and radiographic progression in early RA: results from the SWEFOT trial. Ann Rheum Dis 2015;74:1102–9.
[99] Schneider M. Target therapy in SLE. Autoimmun Rev 2019;18:21–4.
[100] Sacre K, Criswell LA, McCune JM. Hydroxychloroquine is associated with impaired interferon-alpha and tumor necrosis factor-alpha production by plasmacytoid dendritic cells in systemic lupus erythematosus. Arthritis Res Ther 2012;14:R155.
[101] Silva JC, Mariz HA, Rocha Jr. LF, Oliveira PS, Dantas AT, Duarte AL, et al. Hydroxychloroquine decreases Th17-related cytokines in systemic lupus erythematosus and rheumatoid arthritis patients. Clinics (Sao Paulo) 2013;68:766–71.
[102] Willis R, Seif AM, McGwin Jr. G, Martinez-Martinez LA, Gonzalez EB, Dang N, et al. Effect of hydroxychloroquine treatment on pro-inflammatory cytokines and disease activity in SLE patients: data from LUMINA (LXXV), a multiethnic US cohort. Lupus 2012;21:830–5.