Title:

An evaluation of voclosporin for the treatment of lupus nephritis

Authors:

Fang En Sin[1]

David Isenberg[2]

[1]Rheumatology Department, University College Hospital London, 250 Euston Road, London, NW1 2PG

[2]Centre for Rheumatology, Division of Medicine, University College London, 424 The Rayne Building, 5 University Street, London, WC1E 6JF

Corresponding author:

Fang En Sin

Rheumatology Department, University College Hospital London, 3rd Floor, 250 Euston Road, London, NW1 2PG

Email: fangen.sin1@nhs.net

Telephone number: 02034477710

Abstract

Introduction: Lupus nephritis (LN) is associated with significant morbidity and mortality. Current treatment outcomes remain suboptimal. No disease modifying medications are licensed for the treatment of LN. Voclosporin, a novel calcineurin inhibitor, has been investigated as induction therapy in LN in combination with myocophenolate mofetil (MMF) and glucocorticoid (GC). Two Phase II trials of voclosporin were the first trials of a potential treatment for active LN to meet their primary endpoints.

Areas covered: This article reviews the pharmacology of voclosporin and the efficacy and safety data from the two existing phase II trials. In the phase IIb randomised controlled trial AURA-LV, voclosporin was shown to be superior to placebo, when used in combination with MMF (1-2g/day) and GC, in achieving remission in active LN. Of note, 13 deaths (4.9%) were reported over the 48-week trial period, 10 of which occurred in the low dose voclosporin group. This disproportionately high mortality rate may be explained by the higher number of patients with more severe LN, more co-morbidities and with poorer healthcare access being randomised to the low dose voclosporin arm. .

Expert opinion: Whilst the positive outcome of existing trials is promising, further data confirming its efficacy, and evaluating its safety is required. A phase III trial is currently recruiting. Importantly, the positive results were achieved despite a novel and rapid GC taper regime, suggesting that rapid taper of GC may be a viable treatment option in active LN which merits further investigations.

(242 words)

Keywords:

Calcineurin inhibitor

Lupus nephritis

Systemic lupus erythematosus

Voclosporin

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic, multisystem autoimmune rheumatic disease which predominantly affects women of reproductive age. Its prevalence ranges from approximately 40/100,000 in Caucasians to 200/100,000 amongst Afrocarribeans. The survival of patients with SLE has improved over the past 6 decades, with a 15-year survival rate of 0.82 reported between 2008-2016 in the developed world [1], compared to a 5-year survival rate of 0.50 in the 1950's [2]. Nonetheless, this still means that patients have a 1 in 6 chance of dying within 15 years of diagnosis.

Lupus nephritis (LN) is the commonest serious manifestation of SLE. Approximately 30-50% of SLE patients develop clinically evident renal disease [3], up to 11% of whom develop end stage renal failure (ESRF) at five years [4]. LN is a poor prognostic indicator – patients with LN have a nine times higher age- and sex-adjusted mortality ratio, compared to the general population [5]. The risk of premature death increases to 14 and 63 times respectively in the presence of renal damage and ESRF [5]. Importantly, survival improves if remission is achieved [6].

2. Current approach to management of LN

The objective of LN treatment is to improve quality of life and survival by preventing the development of renal damage and ESRF, and to minimise treatment-related complications. Generally, treatment strategy includes an induction phase aimed at attenuating inflammatory activity, followed by a maintenance phase to prevent flares.

Treatment should aim to achieve complete remission (CR). There is no single agreed definition of treatment response for LN, but most of those used include an improvement in proteinuria and normalisation of estimated glomerular filtration rate (eGFR). It is acknowledged that few achieve CR within the induction period, and that clinical improvement continues into the maintenance phase [7,8]. Nevertheless, early response to therapy is predictive of good long term renal outcome. 7-year follow up data from the Euro-Lupus Nephritis Trial (ELNT) showed that a fall in serum creatinine level and a urinary protein creatinine ratio (UPCR) of <1g/24 hours at 6 months [9] or a UPCR <0.8g/24 hours at 12 months [10] were good predictors of long term renal outcome.

To date, no disease modifying medications have been approved in Europe or in the United States for the treatment of LN. Cyclophosphamide (CYC) and mycophenolate mofetil (MMF) are widely used off-label, in line with recommendations from major international guidelines [7,8,11,12]. Despite positive results from many observational studies and registries [13-15], Rituximab failed to meet its primary endpoint in the phase III Lupus Nephritis Assessment with Rituximab (LUNAR) randomised controlled trial (RCT) [16]. The reasons for the failure are debatable. It is possible that the large concomitant doses of glucocorticoid (GC) and immunosupressants used 'raised the bar' too high for Rituximab to demonstrate an additional effect[17]. Rituximab continues to be used off-label in LN. Furthermore, the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) guidelines for LN recommend Rituximab as a viable management option [8,11].

Despite the use of these potent immunosuppressants, the rate of response to treatment remains suboptimal. Across key RCTs in LN (Table 1), treatment response is achieved by only approximately 50% of subjects.

CYC, MMF and long term GC are associated with significant risks of toxicity. The risk of amenorrhoea and infertility with CYC is an important consideration in the young female population most commonly affected by LN. However, no increase in infertility has been reported with the low dose Euro-Lupus regime (6x500mg intravenous (IV) CYC) [18]. Long term GC causes a multitude of side effects especially increased risk of infections, osteoporosis, diabetes and hypertension, which increase the mortality and morbidity of SLE patients.

Thus, the search continues for better treatment of LN, which ideally provides better remission rates, has a more favourable side effect profile and allows early discontinuation of GC.

2.1 Use of calcineurin inhibitors in LN

Calcineurin inhibitors (CNIs), such as Cyclosporin A (CSA) and Tacrolimus (TAC), inhibit T-cell mediated immune response, thereby attenuating the inflammatory process in LN [19]. CNIs bind to and inhibit calcineurin, a calcium-dependant phosphatase, thus preventing T-cell activation and transcription of T-cell mediated cytokines [19]. In addition, CNIs stabilise the actin cytoskeleton in kidney podocytes, leading to reduction in proteinuria [20].

CNIs were first tried in SLE in 1980 when five patients with lupus (two with nephritis) were given 10mg/kg/day of CSA [21]. This resulted in unacceptable side effects and this approach was relatively little used for some years in consequence. However, the British Isles Lupus Assessment Group (BILAG) undertook a comparison of CSA (maximum dose 3.5mg/kg/day) and azathioprine (AZA) and showed that both drugs were effective steroid-sparing agents [22]. 12 out of 47 lupus patients in this study had renal disease [22].

In recent years, various RCTs have demonstrated that CNI is non-inferior to CYC or MMF as an induction therapy of LN [23-25]. Long term data from two of these trials with a mean follow up of 7.7 years (CSA vs CYC) and 5 years (TAC vs MMF) respectively showed no difference in renal function and incidence of ESRF [25,26]. However, a lower rate of renal flares was observed in the MMF induction group compared to the TAC induction group (RR 0.67, 95% CI 0.48 to 0.98) after a mean follow up of 60.8 months [25,27].

In attempts to improve the outcome of LN, treatment strategies combining immunosuppressive agents with different mechanisms of action have been tested. An RCT evaluating the combination of TAC (4mg/day) and MMF (1g/day) concluded that the multi-target regime was superior to IV CYC (0.5-1g/m^2) alone in achieving CR (45.9% vs. 25.6%, p<0.001) at 24 weeks in 368 Chinese patients with active LN [28]. However, a higher rate of serious infections occurred in the multi-target group [28]. An 18-month extension study showed no difference in relapse rates and renal function between both groups [29].

Despite demonstrable efficacy, the use of CNIs is limited by adverse effects such as hirsutism, electrolyte disturbances, hypertension, hyperlipidaemia, diabetes, neurotoxicity and nephrotoxicity. Chronic nephrotoxicity associated with long term CNI, especially CSA use amongst renal and non-renal transplant recipients is a concern [30]. In LN studies,

transient increase in serum creatinine was seen with Tacrolimus induction therapy [25]. However, longer term maintenance studies using CSA did not observe a deterioration of creatinine clearance after a 4-year follow up period [31].The bioavailability of CSA and TAC shows significant inter- and intra-individual variation due to differences in absorption and liver metabolism. This variation and their narrow therapeutic window necessitate regular drug level monitoring and dose adjustment for both these agents.

3. Voclosporin

3.1 Chemical structure, pharmacokinetics and pharmacodynamics

Voclosporin (trans-ISA247) is a derivative of CSA. It has a modified functional side chain (arrow in Figure 1) which induces structural changes in calcineurin, resulting in a 4-fold increase in potency compared to CSA [19]. An animal study showed that a lower blood level of voclosporin was able to produce a greater or similar inhibition of lymphocyte proliferation, expression of T-cell activation surface antigens, and T-cell cytokine production compared to CSA [32].

The side chain also modifies the metabolic profile of voclosporin causing more rapid elimination of its metabolites [33], potentially reducing the risks of CNI adverse effects. A phase IIb renal transplant trial demonstrated a lower incidence of diabetes at 6 months in the low dose (0.4mg/kg b.i.d.) and medium dose (0.6mg/kg b.i.d.) voclosporin groups compared to the TAC group [34].

Unlike CSA and TAC, voclosporin has a more predictable pharmacokinetic and pharmacodynamic profile, which allows for fixed dosing and potentially eliminate the need

for therapeutic drug monitoring [35,36]. A phase III study in plaque psoriasis demonstrated a strong correlation between voclosporin dose, trough blood concentration , clinical efficacy and risk of adverse events (specifically new onset diabetes mellitus [37]. Similarly, another study of voclosporin in kidney transplantation observed a good correlation between voclosporin dose, calcineurin inhibition and drug efficacy [34]. Moreover, pharmacokinetics and pharmacodynamic study in kidney transplant patients demonstrated that weight was not a relevant covariate in drug clearance or distribution, negating the need for weight-based dosing [38].

Voclosporin is extensively metabolised in the liver by the Cytochrome P450 (CYP) 3A4/5 enzyme following oral administration [36]. Voclosporin exposure is influenced by concomitant administration of strong inhibitors and inducers of CYP3A4/5 and inhibitors or substrates of P-glycoprotein [36]. However, unlike CSA, it does not interact with MMF [34], a standard of care (SOC) agent in LN. Voclosporin exposure is also affected by severe renal impairment (1.5 fold increase when GFR <30 ml/min) and mild to moderate hepatic impairment (1.5-2.0 fold increase in Child-Pugh A and B liver disease) [39].

3.2 Voclosporin in LN

Voclosporin has been shown to be an efficacious and safe immunosuppressant in phase IIb and phase III trials in renal transplant recipients and in plaque psoriasis patients, summarised in table 2.

Two phase II trials in LN have been completed (see drug summary box), and a Phase III trial (NCT03021499) is expected to complete recruitment by the end of 2018. A 2-year

extension trial (NCT03597464) to include subjects who achieve complete or partial renal response in the phase III trial has also been planned. .

3.2.1 Phase II trial (AURION)

The AURION trial was a proof-of principle, single arm exploratory trial of voclosporin in 10 patients with active LN. Patients were treated with voclosporin 23.7mg twice a day, in addition to MMF 1-2g/day and GC. All patients had a novel rapid steroid taper to 5mg daily by week-12, and were maintained on 2.5mg daily between week-16 and week-48 [40]. Inclusion criteria and outcome measures of the trial are summarised in Table 3.

Patients treated were all Asian females with a mean age of 28 ± 4.92 years. Three patients had International Society of Nephrology (ISN)/Renal Pathology Society (RPS) Class III LN, two had Class IV, three had Class V whilst one each had Class III/V and Class IV/V disease. Mean eGFR at enrolment was 85.4 ± 3.1 ml/min/1.73m^2, mean UPCR was 1.70 ± 0.43 mg/mg [40].

All patients achieved 25% reduction in UPCR within 8 weeks [40]. At 24 weeks, mean C3 and C4 levels increased by 22% and 58% from baseline respectively [40]. Complete remission was achieved in 7/10 patients by week 24, and 5/7 patients by week 48 (three patients dropped out between week 24 and 48) [40]. eGFR remained stable throughout 48 weeks. Of the three patients who dropped out, two were discontinued due to non-renal SLE flare and infections, one due to fever of unknown origin. Treatment-related adverse events included raised blood pressure in one patient and hirsutism in another, both of which resolved upon voclosporin dose reduction [41].

The authors concluded that the study was supportive of voclosporin use as part of a multi-target therapy approach in conjunction with MMF and GC for the treatment of LN, and that voclosporin was well-tolerated [40].

3.2.2 Phase IIb randomised controlled trial (AURA-LV)

Following the positive AURION trial, a randomised double-blind placebo-controlled multi-centre study, AURA-LV was conducted to assess if voclosporin, in addition to SOC (MMF and GC), increases the speed of remission and rate of remission whilst allowing a low cumulative steroid exposure [35].

265 patients with active LN from 20 countries were randomised into three arms: placebo, low dose voclosporin (23.7mg twice daily) and high dose voclosporin (39.5mg twice daily), in addition to MMF 2g/day and GC. Just like the AURION trial, the dose of prednisolone was rapidly tapered from 20-25mg daily to 5mg daily by week 7 and maintained at 2.5mg daily from week 16. Key trial characteristics and outcome measures are presented in Table 4.

Patients treated were mostly females (87%) aged between 18 and 66 (mean 31.7 ± 10.5). A heterogenous ethnicity was included – 40% patients were Caucasians, 5.3% Blacks, 22.6% Indian sub-continent Asians and 27.2% other Asians. 13% were of Hispanic or Latino origin [35]. 15% had pure ISN/RPS Class V LN. 67% had only Class III or IV disease whilst a further 17% had Class III or IV plus Class V disease [35]. The mean eGFR was 100 ± 27.8ml/min/1.73m^2, whilst the mean UPCR was 4.7 ± 3.62mg/mg [33].

The trial met its primary endpoint. At 24 weeks, the rate of CR was significantly higher in the low dose group compared to the placebo group (32.6% vs 19.3%, OR 2.03, *p*=0.045) [35]. The high dose group had a numerically higher CR rate (27.3%) compared to placebo, although the difference was not statistically significant (*p*=0.204) [42].

The trial also achieved most of its secondary outcomes (where reported so far), which are summarised in table 5. Both low dose and high dose voclosporin were superior to placebo in time to CR and time to PR (Figure 2) [35]. Both the high dose and low dose groups achieved a significantly greater reduction in anti-dsDNA antibody levels compared to controls at 48 week [33].

Importantly, the positive trial outcome was achieved with a rapid taper of GC. A prednisolone dose of ≤2.5mg daily was achieved by 71%, 76% and 75% of patients in the placebo, low dose and high dose arm respectively by week 16 [43].

3.3 Safety and tolerability

Over 92% of patients from the AURA-LV trial experienced at least one adverse event (AE), with infection being the commonest (55% low dose, 66% high dose, 55% placebo) [35]. The rate of serious adverse events (SAE) was numerically higher in the treatment arms (28% low dose, 25% high dose and 19% placebo) [35]. Overall, 13 deaths were reported (4.9%). 10 deaths occurred in the low dose group (infection three, acute respiratory distress syndrome two, thrombosis three, cardiac tamponade one, pulmonary haemorrhage one), two in the high dose group (infection, pulmonary embolism) and one in the placebo group (cerebrovascular accident) during the 48-week treatment period [35].

No change in eGFR, electrolytes and blood pressure were seen in all patients in the treatment arms [33].

The investigators concluded that voclsoporin in combination with MMF was effective in the treatment of LN, despite aggressive tapering of steroids. The higher SAE rates in treatment groups were attributed by investigators to general immunosupression rather than a direct result of voclosporin [35].

3.4 Conclusion

The new generation CNI voclosporin, in addition to SOC (MMF and GC), appears to be efficacious in inducing CR within 24 weeks in LN based on the existing two Phase II trials [35,40]. However, these trials also raise some concerns, primarily regarding the adverse events seen in AURA-LV that need to be addressed in future studies.

The disproportionately high death rate in the AURA-LV low dose voclosporin group even when compared to the high dose group suggests that mortality may not be directly linked to drug exposure but rather to other factors. The published data of previous voclosporin trials, which included a total of 1082 patients with psoriasis or post-renal transplantation, have not highlighted any signal of drug-related fatality (Table 2). A 60-week follow up study of voclosporin (0.8mg/kg/day) in plaque psoriasis reported no deaths [44].

Possible explanations include that by chance, a higher proportion of patients with more severe LN [35] or with more co-morbidities were randomised into the low dose group. It may also be that access to medical care of those in the low dose group was not as good as

those in the high dose group, again by chance. In fact, 11/13 deaths reported occurred in less developed countries, namely Bangladesh (seven), Philippines (two) and Sri Lanka (two) [35]. Nonetheless, more safety data will be needed in the upcoming phase III trial to reassure regulators of the safety of voclosporin in LN.

In the AURA-LV study, a higher dose of voclosporin did not appear to offer superior efficacy to the lower dose in inducing remission [35]. This lack of dose-response relationship may be due to a ceiling effect of drug exposure. Heterogeneity between treatment groups may also be a factor, given that the low dose group included more patients with more severe renal disease [35].

4. Expert opinion

The positive outcome of both these trials is promising, not least because they are the first trials of a potential treatment for active LN to meet their primary endpoints. They also demonstrated that it is possible to achieve improved outcome over current standard of care (SOC), in terms of improved remissions rates and reduced GC exposure.

The rapid GC tapering protocol used in both trials is especially noteworthy. Even in the placebo (SOC) arm, 71% of patients remained on ≤2.5mg prednisolone from week 16 of induction period. This suggests that rapid tapering of steroids in combination with steroid-sparing agents is a potentially viable induction treatment strategy that merits further investigation.

The trials may support the view that multi-target therapy, first investigated in Chinese patients using a combination of TAC, MMF and GC [28], is an option for induction in LN. The international AURA-LV trial provides evidence that multi-target therapy can also be useful in patients from other ethnic backgrounds.

The major potential advantages of voclosporin over existing CNIs are its more predictable pharmacokinetics and pharmacodynamics, which obviate the need for therapeutic drug monitoring. This in turn may allow for wider adoption by physicians and better acceptability by patients, and potentially translate to reduced treatment costs. The other potential benefit is a predicted improved drug safety profile compared to existing CNIs, though this has not been clearly demonstrated in studies to date.

Important questions pertaining to the safety and long term outcomes of the multi-target induction therapies with voclosporin still need to be addressed in further studies including the phase III AURORA trial. Apart from shedding more light on the unexpectedly higher death rates seen in the AURA-LV trial, the increased immunosuppressive risk of the addition of voclosporin to SOC needs to be fully examined. The Chinese trial on TAC versus placebo, in combination with MMF and GC, reported a higher rate of serious infection in the TAC group [28].

In addition, two out of 10 patients from the AURION trial experienced unwanted CNI metabolic side effects (raised blood pressure and hirsutism). More detailed analysis is needed to determine if there is indeed a lower risk of metabolic side effects in voclosporin, compared to TAC and CSA. In order to justify the risk of additional immunosupression with voclosporin use, its superiority over SOC in long term outcomes such as preservation of renal function and improved life expectancy needs to be proven. Liu et al. reported

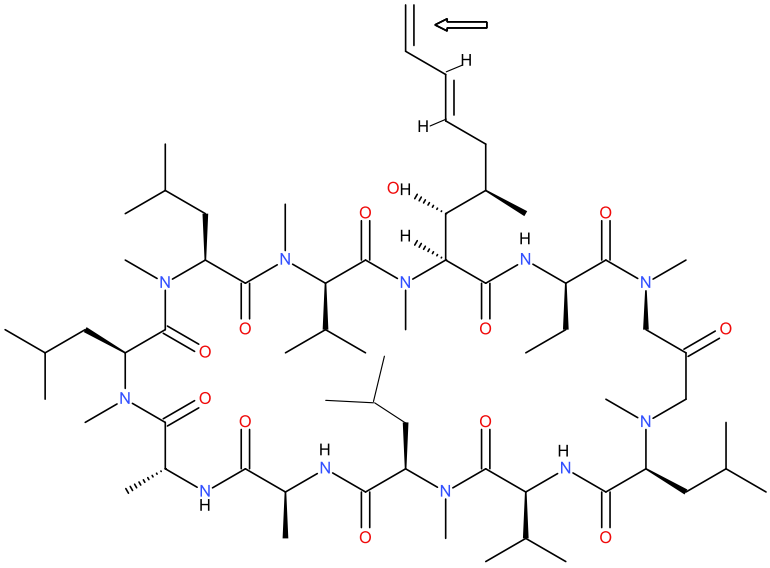
superior efficacy in remission induction using multi-target therapy of TAC, MMF and GC, compared to CYC and GC [28]. However, the 18-month extension trial of the study showed no difference in cumulative flare rates and serum creatinine levels [29].

A possible explanation for the disparity between improved induction rates, but unchanged long term outcome with TAC, is that CNIs also reduce proteinuria via direct effects on podocytes, independent of their immunomodulatory effects in reducing renal inflammation. It is possible that improved proteinuria levels may not be an accurate surrogate marker for renal inflammation when CNIs are used. Further information, such as resolution of active urinary sediment, or improvement in inflammatory index in follow-up renal biopsies would be desirable to support an immunomodulatary effect of voclosporin in LN.

It is important to note that the AURA-LV trial included relatively few Afro-Carribean patients with LN, who generally have poorer response and poorer outcomes. Preliminary subgroup analysis data showed a consistent response to voclosporin across all ethnic groups, including the Black subgroup [45]. The investigators acknowledged that AURA-LV was not powered to demonstrate statistical significance in ethnic subgroups, and that data on potential differential racial response will be addressed in the phase III trial [45]. In summary, the success of voclosporin phase II trials is encouraging, because of the higher and quicker rate of achieving remission compared to SOC. However, its benefit over SOC in achieving important long term outcomes such as renal function preservation and life expectancy is not yet confirmed. Furthermore, the high mortality rate seen in the AURA-LV trial requires further exploration. Another key message borne out of the success of these

trials is the potential for rapid GC taper in induction strategy for LN, which merits further investigation.

Drug summary box

Drug name Voclosporin (trans-ISA247)
Phase Phase II trials completed Phase III trial recruiting
Indication Active lupus nephritis (ISN/RPS Class III, IV and V)
Pharmacology description/ mechanism of action Inhibits T-cell mediated immune response by inhibiting calcineurin Stabilises actin cytoskeleton in kidney podocytes
Route of administration Oral
Chemical Structure  Adapted from National Center for Biotechnology Information. PubChem Compound Database; CID=6918486, https://pubchem.ncbi.nlm.nih.gov/compound/6918486 (accessed June 18, 2018)
Pivotal trial(s) Phase II proof-of-principle trial (AURION) [40] Phase IIb multi-centre randomised, placebo controlled trial (AURA-LV) [33,35,41,42]

Trial/ Study	Number of patients	Drug(s) used	Glucocorticoids	Outcome measures	Results	Reference
ELNT – Euro-Lupus Nephritis Trial	90	High dose CYC (monthly pulses, dose adjusted according to WBC nadir) vs. low dose CYC (500mg every 2 weeks)	Three times 750mg methylprednisolone followed by 0.5mg/kg/day prednisolone for 4 weeks, tapered to maintenance dose 5 to 7mg/day	Treatment failure, defined by one of the following: - Absence of primary response* after 6 months - Occurrence of GC resistant flare - Doubling of serum creatinine level over the lowest value achieved. *Absence of primary response = failure of serum creatinine to improve by a pre-defined level, or persistence of nephrotic syndrome at 6 months. Secondary end point included renal remission, defined as - <10 RBC/hpf - A urinary protein <1g/24hr - Absence of a doubling of the serum creatinine level	Similar treatment failure rate in high dose and low dose CYC groups. 71% low dose and 54% high dose achieved remission at any time during the 41-month follow up (not statistically significant). 27% and 29% flared.	Houssiau et al. 2002 [46]
ALMS – Aspreva Lupus Management Study	370	MMF (3 g/day) vs. IV CYC (0.5 to 1.0 g/m2)	Prednisolone 60mg followed by taper.	Response defined as - Decrease in UPCR to < 3 if baseline >3 - Decrease in UPCR >50% if baseline <3 - Stabilisation (±25%) or improvement in serum creatinine Complete remission defined as normalisation of serum creatinine, urinary protein <0.5g/day and inactive urinary sediment.	No difference in response rate between MMF and IV CYC groups. 56% and 53% in MMF and CYC groups reached primary end point at 24 weeks respectively. 8% achieved complete remission at 6m in both groups	Appel et al. 2009 [47]

LUNAR – Lupus nephritis assessment with rituximab study	144	Rituximab vs. placebo, in addition to MMF (3g/day) and GC	Two times methylprednisolone 100mg with each Rituximab/ placebo, and prednisolone 0.75mg/kg/day until day 16 followed by taper to ≤10mg/day by week 16	Complete renal response defined as normal serum creatinine, inactive urinary sediment, or UPCR <0.5 Partial renal response defined as serum creatinine <115% baseline, urinary RBC s/hpf ≤50% above baseline, no RBC casts and ≥50% decrease in UPCR or to <1.0 if baseline ≤3.0 or to ≤3.0 if baseline >3.0	No difference in renal response rate with addition of Rituximab. 45.8% and 56.9% in placebo and treatment arm achieved complete or partial renal response at week 52.	Rovin et al. 2012 [16]
ACCESS - Abatacept and Cyclophosphamide Combination Efficacy and Safety Study	134	Abatacept vs placebo in addition to Euro-Lupus CYC	Prednisolone 60mg daily for two weeks, followed by taper to 10mg daily over subsequent 10 weeks.	Complete response at 24 weeks, defined as - Stable or improved eGFR - UPCR <0.5 - Prednisolone tapered to ≤10mg daily by week 12	No difference in efficacy with addition of Abatacept. 33% and 31% in treatment group and placebo group respectively achieved complete response at 24 weeks.	Askanase et al. 2014 [48]

Table 1: Summary of key randomised controlled trials of lupus nephritis treatment. CYC: cyclophosohamide, WBC: white blood cells, GC: glucocorticoid, RBC: red blood cells, hpf: high-power field, IV: intravenous, UPCR: urinary protein creatinine ratio, MMF: mycophenolate mofetil, eGFR: estimated glomerular filtration rate.

Trial/ Study	Patients	Voclosporin dose	Comparator drug	Duration	Results	Reference
Phase IIb multi-centre randomised blinded placebo controlled study	201 patients with plaque psoriasis involving at least 10% body surface area	2 groups - 0.5mg/kg/day - 1.5mg/kg/day	Placebo	12 weeks	Voclosporin was efficacious in plaque psoriasis. A dose dependant increase in efficacy was demonstrated. No difference in adverse effect was seen in the lower dose group compared to the placebo group. A rise in creatinine was seen in the higher dose group, although creatinine level remained within normal range.	Bissonnette et al. 2006 [49]
Phase III multi-centre, blinded controlled study	451 patients with plaque psoriasis involving at least 10% body surface area	3 groups - 0.2mg/kg b.i.d - 0.3mg/kg b.i.d - 0.4mg/kg b.i.d	Placebo	Treatment for 12 weeks, monitoring up to 24 weeks	Voclosporin 0.3mg/kg and 0.4mg/kg twice a day were more efficacious than placebo. Approximately 50% and 39% of those in treatment groups and in placebo group respectively had treatment related adverse events, the majority of which were mild-moderate. Eight voclosporin treated patients had a transient reduction in GFR.	Papp et al. 2008 [37]
Phase IIa randomised, multi-centre, open label switching study	96 stable kidney transplant recipients	CSA switched to voclosporin, dose titrated to target trough concentration (mean dose 0.65 ± 0.29 mg/kg)	CSA, dose titrated to target trough concentration (mean dose 1.1 ± 0.2 mg/kg)	12 weeks	Low incidence of acute rejection and stable kidney function were maintained after switching. Voclosporin produced equivalent level of immunosupression at 33% blood drug concentration compared to CSA. Strong correlation between drug exposure and calcineurin inhibition seen with voclosporin but not CSA.	Yatscoff et al. 2003 [50]
Phase IIb multicentrem randomised, open label trial	334 low risk *de novo* kidney transplant patients	3 groups - 0.4mg/kg b.i.d. - 0.6mg/kg b.i.d. - 0.8mg/kg b.i.d. with subsequent dose optimisation to target trough concentration	TAC 0.05mg/kg twice a day with subsequent dose optimisation to target trough concentration	6 months	Incidence of biopsy-proven acute rejection in voclosporin was non-inferior to tacrolimus. Incidence of new onset diabetes in the low and medium voclosporin groups were lower than that of TAC. GFR was statistically lower in the high dose voclosporin group	Busque et al. 2011 [34]

Table 2: Summary of key voclosporin clinical trials in plaque psoriasis patients and renal transplant recipients. B.i.d: bis in die (twice a day), CSA: ciclosporin, GFR: glomerular filtration rate, TAC: tacrolimus.

Trial design	Single arm, twin centre, proof-of-principle trial
Inclusion criteria	1. SLE diagnosed by revised American College of Rheumatology (ACR) criteria 2. ISN/ RPS Class III, IV or V LN from renal biopsy within 24 months 3. Presence of proteinuria (UPCR ≥ 1.0 mg/mg Class III/IV or ≥ 1.5mg/mg Class V) 4. Serological evidence of active SLE 5. eGFR >45 ml/min/1.73m^2
Intervention	Voclosporin (23.7mg twice a day), MMF (1-2g daily) and GC* *GC: 2x 250-500mg IV methylprednisolone followed by prednisolone 25mg or 20mg according to weight, rapid taper to 5mg daily by week 12, and 2.5mg daily between week 16 and week 48.
Primary outcome measures	1. 25% reduction of UPCR, and 2. Normalisation of C3, C4 and anti-dsDNA antibody levels at week 8, and 3. Number of these patients achieving complete remission at week 24.
Secondary outcome measures	Complete remission rate at week 24 and week 48.
Definition of remission	Complete remission defined as • UPCR ≤0.5mg/mg, and • eGFR ≥60ml/min/1.73m^2 or <20% decrease from baseline eGFR

Table 3: Voclosporin AURION phase II proof-of-principle trial characteristics (NCT02949973) [40,41]. SLE: systemic lupus erythematosus, ISN: International Society of Nephrology, RPS: Renal Pathology Society, UPCR: urinary protein creatinine ratio, IV: intravenous, eGFR: estimated glomerular filtration rate, GC: glucocorticoid.

Trial design	Randomised, double-blind placebo-controlled multi-centre study
Inclusion criteria	1. Diagnosis of SLE according to the ACR criteria 2. Biopsy proven ISN/RPS Class III, IV or V LN within 6 months 3. Active nephritis defined as • UPCR ≥ 1.5 mg/mg if Class III/IV LN • UPCR ≥ 2mg/mg if Class V LN (alone or in combination with Class III/ IV)
Intervention	3 arms: 1. Placebo 2. Low dose voclosporin (23.7mg twice daily) 3. High dose voclosporin (39.5mg twice daily) 4. All in addition to MMF 2g/day and GC*. *GC: 25-20mg/day for 2 weeks, tapered to 5mg/day by week 7 and to 2.5mg/day between week 13 and week 48.
Primary outcome measure(s)	Proportion of subjects achieving complete remission at 24 weeks
Secondary outcome measures	1. Complete remission rate at 48 weeks. 2. Partial remission rate at 24 and 48 weeks. 3. Time to complete remission. 4. Time to partial remission. 5. Durability of remission. 6. Extra-renal activity as assessed by SLEDAI at 24 and 48 weeks.
Trial definitions of remission	Complete remission defined as the composite of: • UPCR ≤ 0.5mg/mg • eGFR >60 ml/min/1.73m^2 or within 20% of baseline, • Presence of sustained low dose steroids (Prednisolone ≤10mg daily week 16-48) • No administration of rescue medications Partial remission defined as • 50% reduction in UPCR from baseline, and • No use of rescue medications.

Table 4: Voclosporin AURA-LV phase IIb randomised controlled trial characteristics (NCT02141672) [35,42]. SLE: systemic lupus erythematosus, ACR, American College of Rheumatology, ISN: International Society of Nephrology, RPS: Renal Pathology Society, UPCR: urinary protein creatinine ratio, MMF: mycophenolate mofetil, GC: glucocorticoid, SLEDAI: Systemic Lupus Erythematosus Disease Activity Index, eGFR: estimated glomerular filtration rate.

Study endpoints	Placebo group	Low dose group	High dose group
Complete remission rate at 24 weeks*	19.3%	32.6% (*p*=0.045)	27.3% (*p*=0.204)
Complete remission rate at 48 weeks#	23.9%	49.4% (*p*<0.001)	39.8 (*p*=0.026)
Partial remission at 24 weeks#	49%	70% (*p*=0.007)	66% (*p*=0.024)
Extra-renal activity reduction from baseline, as assessed by SLEDAI at 24 weeks#+	-2.6	-3.0	-3.4

Table 5: Results of primary* and secondary# outcome measure of the AURA-LV trial (all *p*-values were between treatment arm and placebo arm). Partial remission rate at 48 weeks, extra-renal activity as assessed by SLEDAI (Systemic Lupus Erythematosus Disease Activity Index) at 48 weeks and durability of remission are still unreported. +no statistical analyses reported. [35,42]

References

1. Tektonidou MG, Lewandowski LB, Hu J, et al.: **Survival in adults and children with systemic lupus erythematosus: A systematic review and bayesian meta-analysis of studies from 1950 to 2016.** *Annals of the rheumatic diseases* (2017) annrheumdis-2017-211663.

2. Merrell M, Shulman LE: **Determination of prognosis in chronic disease, illustrated by systemic lupus erythematosus.** *Journal of chronic diseases* (1955) **1**(1):12-32.

3. Almaani S, Meara A, Rovin BH: **Update on lupus nephritis.** *Clinical Journal of the American Society of Nephrology* (2017) **12**(5):825-835.

4. Tektonidou MG, Dasgupta A, Ward MM: **Risk of end-stage renal disease in patients with lupus nephritis, 1971–2015: A systematic review and bayesian meta-analysis.** *Arthritis & Rheumatology* (2016) **68**(6):1432-1441.

5. Mok C, Kwok RC, Yip PS: **Effect of renal disease on the standardized mortality ratio and life expectancy of patients with systemic lupus erythematosus.** *Arthritis & Rheumatology* (2013) **65**(8):2154-2160.

6. Chen YE, Korbet SM, Katz RS, et al.: **Value of a complete or partial remission in severe lupus nephritis.** *Clinical Journal of the American Society of Nephrology* (2008) **3**(1):46-53.

7. Group KDIGO: **Kdigo clinical practice guideline for glomerulonephritis.** *Kidney International Supplements* (2012) **2**(139-274.

8. *Bertsias GK, Tektonidou M, Amoura Z, *et al*: **Joint european league against rheumatism and european renal association-european dialysis and transplant association (eular/era-edta) recommendations for the management of adult and paediatric lupus nephritis.** *Annals of the Rheumatic Diseases* (2012) **71**(11):1771-1782.

   Key European guideline on the management of lupus nephritis.

9. Houssiau FA, Vasconcelos C, D'cruz D, 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 & Rheumatology* (2004) **50**(12):3934-3940.

10. Dall'Era M, Cisternas MG, Smilek DE, et al.: **Predictors of long-term renal outcome in lupus nephritis trials: Lessons learned from the euro-lupus nephritis cohort.** *Arthritis & rheumatology* (2015) **67**(5):1305-1313.

11. *Hahn BH, McMahon MA, Wilkinson A, *et al*: **American college of rheumatology guidelines for screening, treatment, and management of lupus nephritis.** *Arthritis Care and Research* (2012) **64**(6):797-808.

Key American guideline on the managemetn of lupus nephritis.

12. Ruiz-Irastorza G, Espinosa G, Frutos MA, et al.: **Diagnosis and treatment of lupus nephritis: Consensus document from the systemic auto-immune disease group (geas) of the spanish society of internal medicine (semi) and the spanish society of nephrology (s.E.N.).** *Nefrologia* (2012) **32**(SUPPL. 1):1-45.

13. Catapano F, Chaudhry AN, Jones RB, et al.: **Long-term efficacy and safety of rituximab in refractory and relapsing systemic lupus erythematosus.** *Nephrology Dialysis Transplantation* (2010) **25**(11):3586-3592.

14. Pepper R, Griffith M, Kirwan C, et al.: **Rituximab is an effective treatment for lupus nephritis and allows a reduction in maintenance steroids.** *Nephrology Dialysis Transplantation* (2009) **24**(12):3717-3723.

15. Terrier B, Amoura Z, Ravaud P, et al.: **Safety and efficacy of rituximab in systemic lupus erythematosus: Results from 136 patients from the french autoimmunity and rituximab registry.** *Arthritis & Rheumatology* (2010) **62**(8):2458-2466.

16. Rovin BH, Furie R, Latinis K, et al.: **Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: The lupus nephritis assessment with rituximab study.** *Arthritis & Rheumatology* (2012) **64**(4):1215-1226.

17. Ramos L, Isenberg D: **Rituximab: The lupus journey.** *Current Treatment Options in Rheumatology* (2015) **1**(1):30-41.

18. Houssiau F: **Thirty years of cyclophosphamide: Assessing the evidence.** *Lupus* (2007) **16**(3):212-216.

19. Kuglstatter A, Mueller F, Kusznir E, et al.: **Structural basis for the cyclophilin a binding affinity and immunosuppressive potency of e-isa247 (voclosporin).** *Acta Crystallographica Section D: Biological Crystallography* (2011) **67**(2):119-123.

20. Faul C, Donnelly M, Merscher-Gomez S, et al.: **The actin cytoskeleton of kidney podocytes is a direct target of the antiproteinuric effect of cyclosporine a.** *Nature medicine* (2008) **14**(9):931.

21. Isenberg D, Snaith M, Morrow W, et al.: **Cyclosporin a for the treatment of systemic lupus erythematosus.** *International journal of immunopharmacology* (1981) **3**(2):163-169.

22. Griffiths B, Emery P, Ryan V, et al.: **The bilag multi-centre open randomized controlled trial comparing ciclosporin vs azathioprine in patients with severe sle.** *Rheumatology* (2010) **49**(4):723-732.

23. Hannah J, Casian A, D'Cruz D: **Tacrolimus use in lupus nephritis: A systematic review and meta-analysis.** *Autoimmunity reviews* (2016) **15**(1):93-101.

24. Zavada J, Pešickova S, Ryšavá R, et al.: **Cyclosporine a or intravenous cyclophosphamide for lupus nephritis: The cyclofa-lune study.** *Lupus* (2010) **19**(11):1281-1289.

25. Mok CC, Ying KY, Yim CW, et al.: **Tacrolimus versus mycophenolate mofetil for induction therapy of lupus nephritis: A randomised controlled trial and long-term follow-up.** *Annals of the rheumatic diseases* (2014) **75**(1):30-36.

26. Zavada J, Pešičková SS, Ryšavá R, et al.: **Extended follow-up of the cyclofa-lune trial comparing two sequential induction and maintenance treatment regimens for proliferative lupus nephritis based either on cyclophosphamide or on cyclosporine a.** *Lupus* (2014) **23**(1):69-74.

27. Tunnicliffe DJ, Palmer SC, Henderson L, et al.: **Immunosuppressive treatment for proliferative lupus nephritis.** *Cochrane Database of Systematic Reviews* (2018) 6).

28. Liu Z, Zhang H, Liu Z, et al.: **Multitarget therapy for induction treatment of lupus nephritis: A randomized trial.** *Annals of internal medicine* (2015) **162**(1):18-26.

29. Zhang H, Liu Z, Zhou M, et al.: **Multitarget therapy for maintenance treatment of lupus nephritis.** *Journal of the American Society of Nephrology* (2017) **28**(12):3671-3678.

30. Naesens M, Kuypers DR, Sarwal M: **Calcineurin inhibitor nephrotoxicity.** *Clinical journal of the American Society of Nephrology : CJASN* (2009) **4**(2):481-508.

31. Moroni G, Doria A, Mosca M, et al.: **A randomized pilot trial comparing cyclosporine and azathioprine for maintenance therapy in diffuse lupus nephritis over four years.** *Clinical journal of the American Society of Nephrology : CJASN* (2006) **1**(5):925-932.

32. Birsan T, Dambrin C, Freitag DG, et al.: **The novel calcineurin inhibitor isa247: A more potent immunosuppressant than cyclosporine in vitro.** *Transplant international : official journal of the European Society for Organ Transplantation* (2005) **17**(12):767-771.

33. **Pendergraft WF, Tumlin J, Rovin BH, et al.: **Aura-lv: Successful treatment of active lupus nephritis with voclosporin.** *American Society of Nephrology Kidney Week 2016, Chicago, IL* (2016).

    Presentation on data from pivotal Phase IIb trial on vocloporin in lupus nephritis.

34. *Busque S, Cantarovich M, Mulgaonkar S, et al.: **The promise study: A phase 2b multicenter study of voclosporin (isa247) versus tacrolimus in de novo kidney transplantation.** *American Journal of Transplantation* (2011) **11**(12):2675-2684.

    Key trial illustrating efficacy and safety of voclosporin as an immunosupressive agent in renal transplantation, compared to tacrolimus.

35. **Dooley M, Pendergraft III W, Ginzler EM, et al.: **Speed of remission with the use of voclosporin, mmf and low dose steroids: Results of a global lupus nephritis study.** *American College of Rheumatology (ACR) 2016 Annual Meeting, Washington D.C.* (2016).

Abstract presenting data from pivotal Phase IIb trial on vocloporin in lupus nephritis.

36. *Ling SY, Huizinga RB, Mayo PR, et al.: **Cytochrome p450 3a and p-glycoprotein drug–drug interactions with voclosporin.** *British Journal of Clinical Pharmacology* (2014) **77**(6):1039-1050.

Study on clinically important pharmacokinetics of voclosporin.

37. *Papp K, Bissonnette R, Rosoph L, et al.: **Efficacy of isa247 in plaque psoriasis: A randomised, multicentre, double-blind, placebo-controlled phase iii study.** *The Lancet* (2008) **371**(9621):1337-1342.

Key trial illustrating efficacy and safety of voclosporin in psoriasis, and also its predictable relationship between drug dose, drug concentration, clinical afficacy and risk of adverse effects.

38. Mayo PR, Ling SY, Huizinga RB, et al.: **Population pkpd of voclosporin in renal allograft patients.** *Journal of clinical pharmacology* (2014) **54**(5):537-545.

39. *Ling S, Huizinga R, Mayo P, et al.: **Pharmacokinetics of voclosporin in renal impairment and hepatic impairment.** *The Journal of Clinical Pharmacology* (2013) **53**(12):1303-1312.

Study on clinically important pharmacokinetics of voclosporin.

40. **Huizinga R, Yahya R, Gafor A, et al.: **Aurion study: 24-week data of multi-target therapy with voclosporin, mmf and steroids for active lupus nephritis.** *Lupus* (2017) **4**(Suppl 1):A10.

Abstract presenting data from pivotal Phase II trial on vocloporin in lupus nephritis.

41. **Yahya R, Gafor A, Huizinga R, et al.: **Ab0419 aurion study: Preliminary results of voclosporin in lupus nephritis.** *Annals of the rheumatic diseases* (2016) **75**(Suppl 2):1049-1050.

Abstract presenting data from pivotal Phase II trial on vocloporin in lupus nephritis.

42. **Dobronravov V, Dooley M, Haq S, et al.: **Lb0002 48 week complete remission of active lupus nephritis with voclosporin.** *Annals of the rheumatic diseases* (2017) **76**(Suppl 2):153.

Abstract presenting data from pivotal Phase IIb trial on vocloporin in lupus nephritis.

43. Tumlin J, Rovin BH, Rahman M, et al.: **Steroid sparing efficacy of voclosporin in active lupus nephritis: Stable kidney function and blood pressure without electrolyte complications at 48 weeks.** *European Renal Association-European Dialysis and Transplant Association Congress, Madrid* (2017).

44. Wasel N, Lynde C, Langley R, et al.: **Long term safety of isa247 in plaque psoriasis after 60 weeks of dosing**

45. Wofsy D, Isenberg DA, Houssiau FA, et al.: **48-week complete remission by ethnic, sex and age subgroups in patients with active lupus nephritis treated with voclosporin. 69**.

46. Houssiau FA, Vasconcelos C, D'Cruz D, *et al*: **Immunosuppressive therapy in lupus nephritis: The euro-lupus nephritis trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide.** *Arthritis and rheumatism* (2002) **46**(8):2121-2131.

47. Appel GB, Contreras G, Dooley MA, et al.: **Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis.** *Journal of the American Society of Nephrology* (2009) **20**(5):1103-1112.

48. Askanase A, Byron M, Keyes-Elstein L, et al.: **Treatment of lupus nephritis with abatacept: The abatacept and cyclophosphamide combination efficacy and safety study.** *Arthritis & rheumatology (Hoboken, NJ)* (2014) **66**(11):3096.

49. Bissonnette R, Papp K, Poulin Y, et al.: **A randomized, multicenter, double-blind, placebo-controlled phase 2 trial of isa247 in patients with chronic plaque psoriasis.** *Journal of the American Academy of Dermatology* (2006) **54**(3):472-478.

50. Yatscoff RW, Abel MD, Aspeslet LJ, et al.: **Phase 2, randomized, multicenter, open-label study of isa247 and neoral® in post-renal transplant patients.** *American Journal of Transplantation Supplement* (2003) **3**(463.