Voclosporin (LUPKYNIS) in Lupus Nephritis
National Drug Monograph
December 2021

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description / Mechanism of Action

- Calcineurin inhibitor (CNI) immunosuppressant.[1] Analogue of cyclosporine (CSA) with more potent calcineurin inhibitory activity in vitro.[2]
- CNIs are believed to work by reducing cytokine production including interleukin-2, thereby reducing activation of immunocompetent lymphocytes, particularly T lymphocytes.[3] CNIs also have a nonimmune antiproteinuric effect by inhibiting calcineurin-mediated destabilization of the cytoskeleton of podocytes and inhibiting podocyte apoptosis.[4]
- Voclosporin is the second drug (after belimumab) and first oral product FDA-approved for lupus nephritis (LN). It is the third CNI (in addition to tacrolimus and cyclosporine) to be used for LN but the only CNI with an FDA indication for LN.

Indication Under Review in This Document

- Treatment of adult patients with active LN in combination with a background immunosuppressive therapy regimen.

Dosage and Administration

- Monitoring Requirements. Before initiating therapy, practitioners should establish an accurate baseline estimated glomerular filtration rate (eGFR) and check blood pressure (BP). eGFR should be assessed every 2 weeks for the first month and every 4 weeks thereafter.
- Initial Dosage: 23.7 mg (three 7.9-mg capsules) orally twice a day as close to every 12 hours as possible and at least 8 hours apart. Subsequent doses should be modified according to eGFR as directed in prescribing information. Reduced initial doses are required for the following situations (refer to prescribing information for details):
    - Severe renal impairment
    - Mild or moderate (Child-Pugh A or Child-Pugh B) hepatic impairment
    - Moderate CYP3A4 inhibitors (e.g., verapamil, fluconazole, diltiazem)
- Interactions with Food. Doses should be taken on an empty stomach. Patients should avoid grapefruit food or drinks during voclosporin therapy.
- Concomitant Therapy. Practitioners should prescribe voclosporin in combination with mycophenolate mofetil (MMF) and glucocorticoids.
- Adequate Trial. If there is no therapeutic benefit by 24 weeks, practitioners should consider discontinuation of voclosporin.
- When NOT to initiate voclosporin. Voclosporin is not recommended in the following situations:

- Patients with a baseline eGFR ≤45 mL/min/1.73 m^2 unless the benefit exceeds the risk; these patients may be at increased risk for acute and/or chronic nephrotoxicity.
- Patients with baseline BP >165/105 mmHg or hypertensive emergency.
- Severe hepatic impairment (Child-Pugh C).
- Concomitant strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin). This is a contraindication.

Dosage Form Under Review

- Capsules: 7.9 mg.
- Packaged as four 3 x 5 blister strips assembled into a cardboard wallet. Available as a single wallet (60 capsules) or carton of three wallets (180 capsules).

Specialty Distribution Medication

- Ordering information is available at PBM Formulary Management - Specialty Distribution Meds - All Documents (sharepoint.com) .

Clinical Evidence Summary

Classification of Lupus Nephritis

- The International Society of Nephrology / Renal Pathology Society (ISN / RPS) categorized LN into six classes).[5,6]

Table 1 ISN / RPS Classification of Lupus Nephritis

Class	Description
I	Minimal mesangial lupus nephritis
II	Mesangial proliferative lupus nephritis
III	Focal lupus nephritis
IV	Diffuse segmental (IV-S) or global (IV-G) lupus nephritis
V	Membranous lupus nephritis
VI	Advanced sclerosing lupus nephritis

Clinical vs Histologic Outcomes

- In the Euro Lupus Nephritis Trial, a combination of decrease in serum creatinine and proteinuria of <1 g/24 hours at 6 months was the best predictor of good long-term (median 73-month) renal outcomes (i.e., not permanently renal impaired (PRI), where PRI was defined as serum creatinine repeatedly ≥1.4 mg/dL.[7] Another study showed that reduction in proteinuria by ≥50% at 6 months predicted 15-year renal survival and patient survival without end-stage renal disease.[8] In the MAINTAIN nephritis trial, the best predictor of long-term renal outcome in patients with LN was proteinuria <0.7 g/24 hours at 12 months.[9]
- However, there is a discordance between clinical response and histologic findings; studies have shown that 30%–50% of complete clinical renal responders had active inflammation on histologic examination despite 6–8 months of immunosuppressive therapy, and 40%–60% of those with no histologic disease activity had high-grade proteinuria.[10,11] Of patients with at least 24 months of clinically quiescent LN after several years of immunosuppressive therapy, 30% had histologic disease activity.[11]

Efficacy Considerations

- The phase 2, dose-ranging AURA-LV randomized clinical trial (RCT) in patients with class III, IV, or V LN showed that voclosporin (23.7 mg vs 39.5 mg twice daily) in combination with mycophenolate mofetil (MMF) was better than placebo plus MMF. The Week-48 complete renal response (CRR) with voclosporin 23.7 mg vs placebo was 49.4% vs 23.9%, respectively (odds ratio [OR] 3.21 [95% CL: 1.68, 6.13]).[12] However, voclosporin had numerically higher rates of serious adverse events and deaths. AURA-LV was considered to be a supportive study to the phase 3 trial.
- The phase 3 Aurinia Renal Response in Active Lupus With Voclosporin (AURORA)-1 RCT confirmed the superiority of combination voclosporin + MMF therapy over MMF + placebo (each therapy given on a background of glucocorticoid [GC] therapy) in achieving CRR, and showed that the combination treatment was efficacious despite rapid taper of glucocorticoids, without the safety concerns seen in AURA-LV.[13]
- A 2-year, double-blind, placebo-controlled, safety and efficacy extension study (AURORA-2) in eligible completers of AURORA-1 is ongoing.

Phase 3 Randomized Clinical Trial: AURORA-1

Study Design

- AURORA-1 was a 52-week, multicenter, double-blind, placebo-controlled RCT that compared voclosporin (23.7 mg twice daily) with placebo on a background of mycophenolate mofetil (MMF, 2 g/d with option to increase to 3 g/d if deemed medically necessary) and glucocorticoids (GCs; methylprednisolone 500 mg (250 mg for weight <45 kg) IV daily for 2 days, then oral prednisone 25 mg (20 mg for weight <45 kg) tapering to ≤2.5 mg/d by Week 16).
    - Protocolled dosage adjustments were made based on eGFR and blood pressure.
    - Protocolled antihypertensive therapy was added to maintain a target blood pressure of ≤130 / ≤80 mm Hg. Study drug was discontinued for systolic blood pressure ≥165 mm Hg and/or diastolic ≥105 mm Hg and was not restarted until discussed with the Medical Monitor.
    - Therapeutic drug monitoring for voclosporin was not performed.
- Major inclusion criteria were age ≥18 and ≤75 years; systemic lupus erythematosus (SLE), biopsy-diagnosed (within previous 6 months) active class III (focal) or IV (diffuse) LN alone or in combination with class V (membranous) LN, or pure class V LN.
    - Active class III/IV LN required confirmed proteinuria ≥1500 mg/24 h and UPCR ≥1.5 mg/mg.
    - Active class V LN required UPCR ≥2 mg/mg.
- Major exclusion criteria included eGFR ≤45 mL/min/1.73 m^2, malignancy within 5 years of screening (except basal and squamous carcinomas treated by excision), lymphoproliferative disease or previous total lymphoid irradiation, severe viral infection within 3 months of screening, and active tuberculosis or known history of tuberculosis.

Efficacy Measures

- Primary Efficacy Measure: CRR at Week 52. This is a composite outcome measure defined as all of the following:
    - Both a urinary protein–creatinine ratio (UPCR) of ≤0.5 mg/mg AND eGFR ≥60 mL/min/1.73 m^2 or no confirmed decrease in eGFR from baseline by >20% or no treatment- or disease-related eGFR-associated event.
    - Completed a protocolled GC taper (i.e., received no more than 10 mg of prednisone equivalent for ≥3 consecutive days or for ≥7 days total during Weeks 44 through Week 52).
    - Did not require use of rescue medication.
- Patients who failed both eGFR measures (i.e., >20% decrease from baseline AND eGFR < 60 mL/min/1.73 m^2) were disqualified from a CRR.

- Key Secondary Efficacy Measures: CRR at Week 24 (CRR with GC dosing assessed from Week 16 to Week 24), time to UPCR ≤0.5 mg/mg, ≥50% decrease from baseline in UPCR (partial renal response) at Weeks 24 and 52, and time to partial renal response.
- A Hochberg step-up statistical procedure was used to control for multiplicity.

Patient Characteristics

- The study population was racially diverse and consisted mainly of young White or Asian females. Average age was 33 years (range, 18–72 years), gender 88% females (12% males), race was mostly White (36.1%) or Asian (30.5%), and ethnicity was Hispanic or Latino in 33% of patients.[3,13]
- Mean duration of SLE was 7 years, and the mean time since diagnosis of LN was about 5 years.[3] The most common LN classification was pure class IV (47%), followed by pure class V (14%), pure class III (13%), class IV/V (13%), and class III/V (12%).[3] The mean (SD) UPCR at baseline was in the nephrotic range (>3 to 3.5 mg/mg)[14]: 4.1 ± 2.7 mg/mg in the voclosporin group and 3.9 ± 2.4 mg/mg in the placebo group.[3] The mean eGFR at baseline was 92 ±31 and 90.4 ± 29, respectively.[3]
- The majority (70%) of patients had hypertension, and 49% had hyperlipidemia.[3]
- Antimalarials (e.g., hydroxychloroquine) were continued after Day 1 in 50% to 60% of patients, and 58% of patients continued ACEI or ARB therapy after study entry.[3] The most common prior treatments were GCs (94%), antimalarials (67%) and MMF (63%).[3]

Results

- A total of 357 patients were randomized: 178 patients to placebo and 179 patients to voclosporin.
- There was an imbalance in the disposition of study patients. By Week 52, the primary efficacy time point, more placebo than voclosporin-treated patients had withdrawn from the study: 31 (17.4%) vs 16 (8.9%), respectively, mostly because of patient withdrawal of consent (7.9% vs 3.9%, respectively).[3] Deaths occurred in 5 (2.8%) and 1 (0.6%) of placebo and voclosporin-treated patients.[3]
- More placebo patients than voclosporin-treated patients discontinued study drug: 59 (33.1%) vs 43 (24.0%), respectively, most commonly because of intolerable adverse events (13.5% vs 12.8%, respectively) and lack of efficacy (6.2% vs 2.2%, respectively).
- Efficacy data are summarized in Table 2.

Table 2 Efficacy results from AURORA-1

Outcome	Time (Wk)	VOC	PBO	Relative Effect (95% CL)	NNT (95% CL)	Q
Primary Efficacy Measure						
CRR at Week 52, n/N (%)	52	73/179 (40.8)	40/178 (22.5)	OR 2.6 (1.6, 4.3)	6 (4, 12)	H
Components of Week-52 CRR						
CRR UPCR ≤0.5 mg/mg, n/N (%)	52	81/179 (45.3)	41/178 (23.0)	OR 3.1 (1.9, 5.0)	5 (4, 8)	H
CRR eGFR success, n/N (%)	52	147/179 (82.1)	135/178 (75.8)	OR 1.5 (0.8, 2.5)	NSD	M†‡
Key Secondary Efficacy Measures						
CRR at Week 24, n/N (%)	24	58/179 (32.4)	35/178 (19.7)	OR 2.2 (1.3, 3.7)	8 (5, 27)	M‡
PRR, n/N (%)	24	126/179 (70.4)	89/178 (50.0)	OR 2.4 (1.6, 3.8)	5 (3, 10)	M†
	52	125/179 (69.8)	92/178 (51.7)	OR 2.3 (1.3, 3.7)	6 (4, 13)	M†
Overall UPCR ≤0.5 mg/mg, n/N (%)	52	116/179 (64.8)	78/178 (43.8)	RR 1.5 (1.2, 1.8)	5 (3, 10)	M†‡
Days to UPCR ≤0.5 mg/mg, median (95% CI)	—	169 (141, 214)	372 (295, NC)	HR 2.0 (1.51, 2.70)	—	H
UPCR-50, n/N (%)	—	173/179 (96.6)	135/178 (75.8)	RR 1.3 (1.2, 1.4)	5 (4, 8)	M†
Days to UPCR-50, median (95% CL)	—	29 (29, 32)	63 (57, 87)	HR 2.1 (1.6, 2.6)	—	H

Sources: 3,13,15

CFB, Change from baseline; H, High; HR, Hazard ratio; M, Moderate; OR, Odds ratio; PEM, Primary efficacy measure; PRR, Partial renal response, defined as ≥50% reduction from baseline in UPCR; Q, GRADE quality of evidence; UPCR, Urinary protein–creatinine ratio; UPCR-50, 50% reduction in UPCR from baseline at any time during the study

† Downgraded for imprecision (optimal information size not met).

‡ Downgraded for imprecision (wide CI).

- The anticipated absolute effect for achieving adjudicated CRR in 52 weeks was 205 (95% CL: 92, 330) more per 1000 patients.
- The CRR benefit was mainly driven by achievement of the UPCR ≤0.5 mg/mg component.[3]
- Secondary efficacy results:
    - Time to UPCR ≤0.5 mg/mg was significantly shorter on voclosporin, with a hazard ratio (HR) of 2.0 (95% CL, 1.51, 2.70).[3] In Kaplan-Meier analyses, the difference between treatments was observed from the first month and was sustained for the rest of the study.
    - Health-related quality of life at Weeks 12, 24, and 52 was evaluated but not reported.[3]
    - Health resource utilization at Weeks 24 and 52 was also evaluated but not reported.[3]

Exploratory Subgroup Analyses

- Although point estimates for Week-52 CRR consistently favored voclosporin in subgroup analyses, results showed no significant treatment differences (95% CL for OR included 1.0) in White patients, the Europe + South Africa and North America regions, class V LN, no use of MMF, and UPCR ≤2 mg/mg.[3]

Network Meta-analyses (Indirect Comparative Efficacy)

- A literature search found a Bayesian network meta-analysis that indirectly compared voclosporin plus MMF, tacrolimus plus MMF, or monotherapy with MMF or cyclophosphamide as induction therapy for lupus nephritis in terms of effectiveness and safety.[16] Based on analyses of four RCTs (two RCTs each for voclosporin plus MMF vs MMF and tacrolimus plus MMF vs IV cyclophosphamide; N = 936), tacrolimus plus MMF was nonsignificantly better than voclosporin plus MMF (OR 1.43; 0.80, 2.57) in achieving complete response. Both tacrolimus plus MMF (OR 2.85; 95% CrI 1.87, 4.39) and voclosporin plus MMF (OR 1.99; 1.35, 2.97) were significantly better than monotherapy. Voclosporin plus MMF was

nonsignificantly safer than tacrolimus plus MMF (OR 0.55; 0.19, 1.48) in the incidence of serious adverse events. Monotherapy was nonsignificantly safer than voclosporin plus MMF (OR 0.80; 0.53, 1.22) and tacrolimus plus MMF (OR 0.44; 0.16, 1.09). Surface under the cumulative ranking curve (SUCRA) values suggested that tacrolimus plus MMF was likely to be the most effective, followed by voclosporin plus MMF then monotherapy, and that monotherapy was likely to be the safest, followed by voclosporin plus MMF then tacrolimus plus MMF. In summary, voclosporin plus MMF was not differentiable from tacrolimus plus MMF as multitarget induction therapy in terms of effectiveness and safety, although it tended to be less effective and safer than tacrolimus plus MMF. Limitations included different monotherapy comparators (MMF vs cyclophosphamide, although they are considered to have similar efficacy); different definitions of complete response; Asian vs multi-ethnic populations (response may be better in Asians); and lack of assessment of relapse risk. The authors disclosed that they had no conflicts of interest.

Safety Considerations

- **AURA-LV**: As mentioned previously, the phase 2 AURA-LV RCT showed numerically higher rates of serious adverse events (26.6% vs 15.9%) and deaths (6.8% vs 1.1%) with voclosporin vs placebo.[3,12] The differences were attributed to imbalances in the regional randomization that allocated a disproportionate number of patients from Asian countries with low gross domestic product to voclosporin (23.7 mg twice daily) and resulted in a bias toward worse safety outcomes.[3]
- **AURORA-1**: The safety signals seen in the phase 2 trial were not confirmed in the phase 3 trial. Serious adverse events occurred in 37 patients (21%) vs. 38 patients (21%) in the voclosporin and placebo groups, respectively.[13] Deaths occurred in 1 patient (<1%) vs 5 patients (3%), respectively.[13]
- **Pooled LN Study Populations** (N = 267 and 266 for voclosporin and placebo, respectively): The safety profile of voclosporin based on up to 52 weeks of data was qualitatively consistent with the known safety profile of other CNIs, with nephrotoxicity and hypertension occurring most commonly.
    - Renal-related adverse events were more common on voclosporin than placebo (33% vs 18%, respectively).[3] The majority of these events consisted of decreases in eGFR (26% vs 9% for voclosporin vs placebo, respectively) that led to dosage modification or discontinuation of study drug.[3]
    - Other known CNI-related adverse events occurred more frequently on voclosporin, such as hypertrichosis, hirsutism, gingival hypertrophy, and tremor.[3]
    - However, quantification of nephrotoxicity remains uncertain.[3] The long-term (>1 y) effects of voclosporin therapy including the risk of chronic CNI-related renal toxicity have not been evaluated to inform whether the short-term proteinuric benefits outweigh potential long-term harms.
- **Boxed Warnings**: Malignancies and serious infections. (Cyclosporine and tacrolimus also have these boxed warnings.)
- **Contraindications**: Concomitant strong CYP3A4 inhibitors, which can significantly increase exposure to voclosporin. (Cyclosporine and tacrolimus lack this contraindication; however, the prescribing information advises avoiding concomitant use of these CNIs with CYP3A4 inhibitors because of the drug interaction.)
- **Other Warnings / Precautions**: Additional warnings include
    - Nephrotoxicity
    - Hypertension
    - Neurotoxicity
    - Hyperkalemia
    - QTc prolongation

- Immunizations: Avoid use of live attenuated vaccines during voclosporin therapy. Inactivated vaccines may fail to provide a sufficient immunogenic response.
- Pure red cell aplasia (PRCA)

- **Deaths and Serious Adverse Events**: No mortality signal was seen in the phase 3 RCT.[3]
  - Deaths: 1 (<1%) vs 5 (3%) on voclosporin vs placebo, respectively.[13]
  - Serious adverse events were more common on voclosporin than placebo, with exposure-adjusted incidence rates of serious adverse events of 32 vs 26 events per 100 patient-years.[3]
  - Specific serious adverse events are summarized in Table 3.

Table 3 Serious adverse events reported during voclosporin clinical trials

Serious Adverse Event	Incidence, pts per 100 PY, VOC 23.7 mg vs PBO	Most Common Types
Infections	11.9 vs 12.0	Pneumonia, gastroenteritis, urinary tract infections
Nephrotoxicity	5.6 vs 3.7	Acute kidney injury and renal impairment
Neurotoxicity	3.9 vs 0.9	Headache, migraine, seizure, and PRES
Hypertension	2.1 vs 0.4	—
Malignancy	1.7 vs 0.0	—

Source: 1

PBO, Placebo; **PRES**, Posterior reversible encephalopathy syndrome; **PY**, Patient-year; **VOC**, Voclosporin

- **Withdrawals Due to Adverse Events (WDAEs)**: In pooled LN data, the incidence of WDAEs were similar in the voclosporin and placebo groups (14% vs 13%, respectively). The most common reason for WDAEs were classified under renal and urinary disorders (including renal impairment, lupus nephritis, and proteinuria), which were less common in the voclosporin group than the placebo group (4% vs 7%, respectively). GFR decreased (4% vs 2%, respectively) and renal impairment (2% vs 2%, respectively) were the most common specific WDAEs.
- **Dosage Modifications Due to Adverse Events (DMDAEs)**: DMDAEs were more frequent on voclosporin than placebo (46% vs 25%, respectively), primarily due to nephrotoxicity and hypertension.[3]
- **Acute Nephrotoxic Adverse Events**: 33% vs 18% of patients on voclosporin vs placebo, respectively, met the definition of Acute Renal Failure Standard MedDRA Queries (SMQ).[3] Acute Renal Failure SMQ adverse events were comprised mainly of decreased GFR (26% vs 9%).[3] Excluding events of decreased GFR, 32 voclosporin-treated patients vs 21 placebo patients experienced Acute Renal Failure SMQ adverse events.[3] More patients on placebo than on voclosporin reported LN as an adverse event.[3]
- **Cardiovascular Adverse Events**: 12% vs 5% on voclosporin vs placebo, respectively.[3] The most common adjudicated cardiovascular event was hypertension (19% vs 9%, respectively).[3]
- **Common Adverse Events** (≥10% in voclosporin group and higher than placebo): GFR decreased (26% vs 9%), hypertension (19% vs 9%), diarrhea (19% vs 13%), headache (15% vs 8%), anemia (12% vs 6%), cough (11% vs 2%), urinary tract infection (10% vs 6%).
- **Other Recognized CNI-related Adverse Events of Interest** (pooled LN data; voclosporin vs placebo,respectively)[3]:
  - Malignancy 2% vs 0%
  - Hypertrichosis 2% vs 0%
  - Hirsutism 2% vs 0%
  - Gingival hypertrophy 2% vs 0%
  - Tremor 3% vs 1%
- **Laboratory Findings of Interest** (pooled LN data; voclosporin vs placebo,respectively)[3]:
  - Hyperlipidemia 3% vs 2%

  - Hypertriglyceridemia <1% vs 3%
  - Hyperglycemia 1% vs 2%
- **Significant Differences in Laboratory Findings**. The voclosporin group showed a significantly greater decrease in **cholesterol** levels.
  - In the pooled LN data, **total cholesterol** levels decreased from baseline to Week 52 to a greater degree on voclosporin than placebo, by 191 mg/dL and 64 mg/dL, respectively.[3] Values entered the normal range (≤200 mg/dL) only in the voclosporin group. The percentage of patients with normal cholesterol by the end of the treatment period increased from baseline to the end of the treatment period by 42 percentage points (17% to 59%) in the voclosporin group and by 29 percentage points (19% to 48%) in the placebo group.[3]
  - In AURORA 1, 82 patients (46%) of the voclosporin group and 92 patients (52%) of the placebo group had hyperlipidemia at baseline. Statin use was not protocolled, and distribution of statin use between the two treatment groups was not reported. Relative to placebo, voclosporin therapy resulted in significantly greater decreases from baseline to Week 52 in **total cholesterol** (least square mean treatment difference, –19.3 [95% CL –32.7, –5.8] mg/dL) and **low-density lipoprotein cholesterol** (–13.7 [–24.4, –2.9] mg/dL).[13]
- **Drug–Drug Interactions.** Voclosporin drug interactions overlap with those for cyclosporine and tacrolimus.
  - **Moderate CYP3A4 inhibitors**: Reduce voclosporin dosage to 15.8 mg in the morning and 7.9 mg in the evening.
  - **Strong and moderate CYP3A4 inducers**: Avoid concomitant use.
  - **Certain P-gp substrates with narrow therapeutic window**: Reduce dosage of substrate as recommended in its prescribing information (voclosporin is a P-gp inhibitor).
  - **OATP1B1 substrates** (e.g., statins): Statins are recommended adjunctive agents to treat hyperlipidemia associated with LN. Monitor for adverse effects from OATP1B1 substrates (voclosporin is an OATP1B1 inhibitor in vitro; not studied clinically).
  - **Lack of interaction with MMF**. Unlike cyclosporine, which may decrease MMF exposure, and unlike tacrolimus, which may increase MMF exposure, voclosporin does not interact with MMF.

Other Considerations

- **Pregnancy**: Unlike alcohol-free cyclosporine formulations and tacrolimus, voclosporin should be avoided in pregnancy (because of its alcohol content, 21.6 mg dehydrated ethanol per capsule or 129.4 mg/d). (Alcohol-containing cyclosporine formulations should be avoided in pregnancy.) There is insufficient data on safety of voclosporin use during pregnancy in humans.
- **Lactation**: Insufficient clinical data.
- **Females and Males of Reproductive Potential**: If voclosporin is used with background mycophenolate mofetil therapy, refer to the prescribing information for mycophenolate mofetil.
- **Therapeutic Drug Monitoring (TDM)**. There are no recommendations for TDM of voclosporin in LN. (For renal transplantation, the proposed therapeutic range is 35 to <60 ng/mL.[17])
- **Pharmacokinetics–Pharmacodynamics**. A study in renal allograft patients showed that voclosporin had less pharmacokinetic–pharmacodynamic (concentration–calcineurin inhibition) variability than cyclosporine.[18] In contrast to cyclosporine, which is metabolized primarily at its amino acid-1 site, voclosporin is primarily metabolized at its amino acid-9 position.[18] Voclosporin is metabolized to IM9, which has ~10% of the parent drug activity and shows anti-T–cell activity equipotent to the AM1 metabolite of cyclosporine, but is produced in much smaller quantities than AM1.[18] The lower production of IM9 with voclosporin relative to AM1 with cyclosporine is believed to result in less competitive antagonism with the parent molecule and less variability in the concentration–calcineurin inhibition

relationship.[18] Although it was theorized that differences in the pharmacokinetic disposition between voclosporin and cyclosporine could potentially result in a better safety profile for voclosporin,[18,19] there is no definite evidence that the pharmacokinetic differences translate into quantitative differences between the two CNIs in clinical safety. Qualitatively, the safety profile of voclosporin is similar to that of cyclosporine.

- **Renal and Hepatic Dosage Adjustments**. Like cyclosporine, and unlike tacrolimus, voclosporin requires dosage adjustment in renal or hepatic impairment; however, only voclosporin has *specific* recommendations for dosage reduction (see prescribing information[1]). All CNIs require dosage reduction for nephrotoxicity.
- **Evidence Gaps.** Health-related quality of life was not reported. Evaluation of voclosporin in African Americans and by other racial groups is needed, considering health disparities in LN prognosis and a potential signal from exploratory subgroup analyses suggesting that voclosporin may be more effective in non-White patients than White patients. Important outcomes not evaluated were histologic response / remission, incidence of end-stage renal disease, requirement for renal replacement therapy, rate of renal transplants, long-term patient survival, hospitalization or readmission, functional ability, and patient satisfaction.

Other Therapeutic Options

- Immunosuppressants play a central role in the prevention of further renal damage, chronic kidney disease, and end-stage renal disease. Immunosuppressive therapy (in combination with glucocorticoids) is indicated for patients with class III (± class V) LN, class IV (± class V) LN, and patients with class V LN with either nephrotic-range proteinuria or proteinuria >1 g/24 hours despite an optimized, adequate trial (for a reasonable time period, such as ≥3 months) of ACEI or ARB therapy.[20,21] Immunosuppressive therapy is unlikely to be effective for class VI LN.
- In addition to immunosuppressants, an angiotension converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) is recommended for all patients with proteinuria or arterial hypertension. Hydroxychloroquine should also be recommended for all patients with LN (class I to V) without contraindications because of its antithrombotic effects[22] and to reduce the risks of developing LN and end-stage renal disease and to improve the likelihood of achieving CRR.[23]
- The general treatment strategy has consisted of *initial* (aka induction) therapy to achieve improvement and *subsequent* (aka maintenance) therapy to prevent renal flares. Sequential immunosuppressive therapy has been conventionally used, with glucocorticoids as the foundation for rapid control followed by addition of other immunosuppressants. Combinations of immunosuppressives have been shown to be effective and are being suggested for initial and subsequent (*continued*) therapy,[24] breaking away from the sequential, induction–maintenance treatment paradigm. Combination therapies include tacrolimus + MMF, voclosporin + MMF, and belimumab + MMF or cyclophosphamide (each concurrently with glucocorticoids).
- Because CNIs (cyclosporin and tacrolimus) have lacked evidence in important areas (non-Asian patients, renal outcomes, and long-term therapy), the 2019 Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR / ERA-EDTA) recommendations for the management of LN did not recommend CNI monotherapy or CNI combination therapy for first-line initial treatment.[20]
- Dosing for CNIs in LN has been inconsistent, using fixed doses or therapeutic drug monitoring (range of target plasma concentrations for tacrolimus: 3–10 ng/mL).[25,26]. The use of CNIs in LN is limited by nephrotoxicity.
    - Duration of an adequate trial of CNIs. In a model-based meta-analysis of 10 clinical studies (N = 222), when a range of tacrolimus concentration of 3–10 ng/mL was used, at least 1.5 months

was needed to optimize efficacy in terms of achieving plateau (80% of maximal) 24-hour changes from baseline in proteinuria in patients with lupus nephritis.[26] The 90% and 95% of maximal changes in urine protein were achieved at 3.33 months and 7.03 months, respectively.

- The American College of Rheumatology last published guidelines for LN in 2012.[21] The most current LN treatment recommendations, developed by EULAR / ERA-EDTA,[20] are summarized in Table 4.

Table 4 2019 EULAR / ERA-EDTA Treatment Recommendations for Lupus Nephritis

Treatment Phase	Class III/IV ± V LN	Class V LN w/ nephrotic-range proteinuria or UPCR >1000 mg/g despite optimal RAAS blocker therapy
Initial Therapy, First-line	**Mycophenolate** (2–3 g/d) + **GC1** OR Low-dose **cyclophosphamide** (ELNT regimen: 500 mg IV q2w for 6 doses) + **GC1**	**Mycophenolate** (2–3 g/d) + **GC2**
Initial Therapy, Alternative	*For All Patients, Including Those at High Risk of Kidney Failure*:† **CNI** (especially TAC 4 mg/d) **+ mycophenolate** (1–2 g/d) + **GC1**, particularly in pts w/nephrotic-range proteinuria *For Patients at High Risk of Kidney Failure*:† High-dose **cyclophosphamide** (NIH regimen: 0.5 to 1 g/m^2 IV once monthly x 6–7 mo) + **GC1**	IV **cyclophosphamide** + **GC2** OR **CNI** (especially TAC) + **GC2** OR **CNI** (especially TAC) **+ mycophenolate** + **GC2**
Subsequent Therapy (for ≥ 3 y)	**Low-dose mycophenolate** (1–2 g/d) OR **Azathioprine** (2 mg/kg/d) – preferred if patient plans to become pregnant. Each therapy + **GC** at lowest possible dose (2.5–5 mg/d) when needed. After at least 3–5 y, tapering / discontinuation of immunosuppressants (GC first) may be attempted if complete response was achieved.	Same as for focal or diffuse LN. Can also consider continuing, switching to, or adding a **CNI** at lowest effective dose.
Active, Refractory LN‡	Switch to one of the alternative initial therapies above (**mycophenolate**, low-dose **cyclophosphamide**, **CNI**, or **CNI + mycophenolate**) OR Switch to **rituximab** (1000 mg on days 0 and 14) monotherapy or in combination with **mycophenolate** or **cyclophosphamide**. A repeat cycle can be considered to prevent or treat relapse. OR Add **belimumab** to mycophenolate or cyclophosphamide.	Switch to another initial therapy (**mycophenolate**, low-dose **cyclophosphamide**, **CNI**, or **CNI + mycophenolate**)

Source: 20

CNI, Calcineurin inhibitor; **ELNT**, Euro-Lupus Nephritis Trial[27]; **GC1**, Glucocorticoid regimen 1 = IV pulses of methylprednisolone (total dose 500–2500 mg) followed by prednisone (0.3–0.5 mg/kg/d) for up to 4 wks, tapered to ≤7.5 mg/d by 3–6 mos; **GC2**, Glucocorticoid regimen 2 = pulse IV methylprednisolone (total 500–2500 mg), then prednisone (20 mg/d, tapered to ≤5 mg/d by 3 mo); **NIH**, National Institutes of Health; **RAAS**, Renin-angiotensin-aldosterone system; **UPCR**, Urine protein–creatinine ratio

† Acute kidney injury / decreased GFR, histologic evidence of cellular crescents, fibrinoid necrosis, or severe interstitial

inflammation

‡ EULAR/ERA-EDTA defines refractory LN as a lack of partial response after 6–12 mos.[28] The KDIGO definition of refractory disease is nonresponse to either MMF or cyclophosphamide used sequentially.[23] The American College of Rheumatology defines refractory LN as worsening nephritis by 3 months or treatment failure as determined by the treating physician by 6 months.[21]

- The Kidney Disease: Improving Global Outcomes (KDIGO) conference summaries[23] are generally consistent with the EULAR / ERA-EDT recommendations.
- CNIs used for the treatment of LN are summarized in Table 5.

Table 5 CNI Immunosuppressive Treatment Alternatives

CNI Regimen / Dosage	Formulary Status for CNI	FDA-approved LN Indication†	Issues for Consideration
Voclosporin (VOC) + MMF + GC PO: 23.7 mg BID initially, then adjust dose based on eGFR	TBD (cap)	Active LN	Unlike CSA and TAC, which were studied in Asians, VOC was shown to be effective in an ethnically diverse population. Unlike non-alcohol CSA formulations and TAC, VOC should be avoided in pregnancy. Unlike TAC, VOC has not been studied in combination with CyP. Types of WPs and AEs for VOC are generally similar to those of CSA and TAC. Recommendations for management of CYP3A4 drug interactions with VOC differ from those with CSA or TAC.
Cyclosporine (CSA) + MMF + GC PO, Refractory LN: CSA 100–150 mg/d (3 mg/kg/d) + MMF 1.5–2.0 g/d[29]	Yes (cap, inj, oral soln)	OLU	Retrospective data.[29] TAC may be preferred over CSA in combination with MMF.[20]
Cyclosporine (CSA) + GC Various PO initial dosage regimens ranging from 2.5–5 mg/kg/d.[30,31,32,33] Then subsequent therapy 2.5–3 mg/kg/d.[30]	Yes (cap, inj, oral soln)	OLU	Low certainty evidence.[37] CSA may have more data in refractory LN than TAC.[34] May be used in pregnancy, except formulations that contain alcohol should be avoided.[45]
Tacrolimus (TAC) + MMF ± GC PO, "multitarget" regimen in class II, III or IV LN (RCT, N = 362): TAC 4 mg/d divided q12h + low-dose MMF 1 g/d divided q12 h + GC.[35] TAC blood concentrations ranged from 5.24 to 5.50 ng/mL.[35] MMF $AUC_{0–12h}$ ranged from 29.57–33.14 mg·h/L. Protocol did not specify target concentrations for either TAC or MMF. PO, "multitarget regimen" in class V+IV LN (RCT, N = 40): TAC 4 mg/d (3 mg/d for weight ≤50 kg) divided q12h + MMF 1 g/d (0.75 g/d for weight ≤50 kg) divided q12h.[36] TAC dosage was titrated to maintain 12-h post-dose trough level of 5–7 ng/mL. MMF was titrated to maintain an $AUC_{0–12h}$ of MPA of 20–45 mg·h/L.	Yes (cap, inj)	OLU	The 2016 pivotal trial showed this "multitarget" regimen to be better than CyP in achieving complete remission at Week 24 (45.9% vs 25.6%, respectively.[35] In a meta-analysis of 2 RCTs (N = 402) of TAC + MMF vs IV CyP, risks for complete remission were 580 (261 to 1000) per 1000 vs 244 per 1000, respectively; RR 2.38, 95% CI 1.07 to 5.30 and anticipated absolute effect 336 more [95% CI 17 to 1048 more] per 1000 people (I^2 = 57%; low certainty evidence).[37] Certainty of evidence for reduction in deaths was very low.

CNI Regimen / Dosage	Formulary Status for CNI	FDA-approved LN Indication†	Issues for Consideration
TAC + CyP + GC PO regimen in 2 RCTs (N = 50 and 45): TAC 3.5 mg/d + CyP 400 mg/m^2 + GC[38]	Same as above	OLU	Limited evidence (2 RCTs with Jadad quality ratings of 3 and 2 out of 5 points).[38] An NMA showed that TAC + CyP was better than CyP, similar to MMF, and nonsignificantly more effective than TAC (each with GC).[38]
TAC + GC Various PO dosage regimens ranging from 0.05–0.2 mg/kg/d divided q12h.[38,39,40,41,42,43] Low-dose PO: 2 mg/d (weight <60 kg) or 3 mg/d (weight ≥60 kg) [44]	Same as above	OLU	Similar to MMF + GC (low certainty evidence) and to IV CyP + GC (low certainty evidence).[37] May be used in pregnancy.[45] TAC is considered to be less nephrotoxic than CSA.[4]

Sources: 3,20,21,34,45,46
Overall response = complete + partial remission.
CNI, Calcineurin inhibitor; **CRR**, Complete renal response; **GC**, Glucocorticoid (e.g., pulse IV methylprednisolone or equivalent 500–1000 mg/d x 3 doses (optional), then oral prednisone or equivalent 0.5–1 mg/kg/d up to maximum 60 mg/d, then taper to ≤5 to 10 mg/d by 3 to 6 mos or minimal effective dose[20,21]); **LN**, Lupus nephritis; **MMF**, Mycophenolate mofetil; **WP**, Warnings and Precautions

Projected Place in Therapy

- **Epidemiology and Prevalence of Lupus Nephritis in Veterans**. SLE is a chronic, multisystem, autoimmune disease that has a prevalence ranging from 20 to 150 cases per 100,000 in the US[47] and about 40 cases per 100,000 in Caucasians to 200 cases per 100,000 in Afro-Caribbeans.[48] It primarily affects women during their reproductive years, making drug-related teratogenicity and infertility important considerations. The majority (65%) of patients with SLE are diagnosed in the age range of 16 to 55 years, and 15% are diagnosed after age 55.[47] LN develops in 50%–60% of patients by 3 years after diagnosis of SLE and is associated with a high risk of renal failure and death.[3] Proliferative subtypes of LN in classes III, IV, or III/IV + V carry the highest risks for development of end-stage renal disease and death. Older age (≥50 years) at onset of disease and male gender are associated with more severe disease, worse outcomes, or higher mortality.[49] Non-white race / ethnicity (African American, Hispanic, and Asian) is associated with more severe presentations and greater organ damage accrual.[49]
- **Potential Place in Therapy Based on the Evidence**. There are no head-to-head or meta-analytic studies to inform whether voclosporin has any efficacy or safety advantages over other CNIs in the treatment of LN. High-quality evidence suggests that, in patients who have active class III ± V or class IV ± V LN with both proteinuria ≥1500 mg/24 h and UPCR ≥1.5 mg/mg or active class V LN with UPCR ≥2 mg/mg, voclosporin has a small to moderate benefit over placebo in achieving complete renal response, or rather that voclosporin in combination with MMF has a small to moderate benefit over standard initial MMF monotherapy. Less than half (40.8%) of the patients reached this end point on voclosporin. The evidence of efficacy and lack of long-term safety including CNI-related nephrotoxicity data support the use of combination voclosporin + MMF as an alternative to MMF as initial therapy, particularly in patients with nephrotic-range proteinuria (at the same level as other CNIs + MMF). Voclosporin was not evaluated as monotherapy, and voclosporin + MMF was not studied in patients with LN refractory to MMF; therefore, its efficacy in these situations is uncertain. The safety data suggested that the adverse effect profile of voclosporin is qualitatively similar to that of other CNIs. The lack of recommendations for therapeutic

drug monitoring with voclosporin in LN is not a clear advantage over other CNIs since monitoring of drug concentrations with cyclosporin or tacrolimus has not been consistently used, and it can help assess medication adherence.[50] Furthermore, optimal drug concentration ranges have not been defined in LN,[50] and the 2019 EULAR / ERA-EDTA guideline made no recommendation for therapeutic drug monitoring with CNIs.[20]

- **Potential Place in Therapy in VHA**. Given an uncertain long-term safety profile and a lack of evidence of significant clinical advantages over other CNIs, voclosporin may be considered as an alternative CNI therapy for LN after cyclosporine or tacrolimus, which are on formulary without criteria for use. An adequate duration of a trial of CNI therapy may be considered to be 2 months. Providers should exercise caution when voclosporin is used longer than one year.[3]

Prepared December 2021. Contact person: Francine Goodman, National PBM Clinical Pharmacy Program Manager, Formulary Management, VA Pharmacy Benefits Management Services (10P4P)

References

[1] LUPKYNIS (voclosporin) capsules [prescribing information online]. Victoria, BC, CA / Rockville, MD: Aurinia Pharmaceuticals. January 2021. Available at: FPI-0011+Approved+USPI++MG.pdf (d1io3yog0oux5.cloudfront.net). Accessed 3 Jun 2021.

[2] Bîrsan T, Dambrin C, Freitag DG, Yatscoff RW, Morris RE. The novel calcineurin inhibitor ISA247: a more potent immunosuppressant than cyclosporine in vitro. Transpl Int. 2005 May;17(12):767-71.

[3] Center for Drug Evaluation and Research (CDER). Multi-discipline review of voclosporin (LUPKYNIS). Food and Drug Administration (FDA). January 2021.

[4] Rafael-Vidal C, Altabás I, Pérez N, Mourino Rodríguez C, Pego-Reigosa JM, Garcia S. Calcineurin and Systemic Lupus Erythematosus: The Rationale for Using Calcineurin Inhibitors in the Treatment of Lupus Nephritis. Int J Mol Sci. 2021 Jan 27;22(3):1263.

[5] Weening JJ, D'Agati VD, Schwartz MM, Seshan SV, Alpers CE, Appel GB, Balow JE, Bruijn JA, Cook T, Ferrario F, Fogo AB, Ginzler EM, Hebert L, Hill G, Hill P, Jennette JC, Kong NC, Lesavre P, Lockshin M, Looi LM, Makino H, Moura LA, Nagata M. The classification of glomerulonephritis in systemic lupus erythematosus revisited. J Am Soc Nephrol. 2004 Feb;15(2):241-50.

[6] Revision of the International Society of Nephrology/Renal Pathology Society classification for lupus nephritis: clarification of definitions, and modified National Institutes of Health activity and chronicity indices. Bajema IM, Wilhelmus S, Alpers CE, et al. Kidney Int. 2018;93:789–796.

[7] 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 Rheum. 2004;50 (12):3934–3940.

[8] Korbet SM, Lewis EJ. Severe lupus nephritis: the predictive value of a >/= 50% reduction in proteinuria at 6 months. Nephrol Dial Transplant. 2013;28(9):2313–2318.

[9] Tamirou F, Lauwerys BR, Dall'Era M, Mackay M, Rovin B, Cervera R, Houssiau FA; MAINTAIN Nephritis Trial Investigators. A proteinuria cut-off level of 0.7 g/day after 12 months of treatment best predicts long-term renal outcome in lupus nephritis: data from the MAINTAIN Nephritis Trial. Lupus Sci Med. 2015 Nov 12;2(1):e000123.

[10] Zickert A, Sundelin B, Svenungsson E, Gunnarsson I. Role of early repeated renal biopsies in lupus nephritis. Lupus Sci Med. 2014;1(1): e000018.

[11] Alvarado AS, Malvar A, Lococo B, et al. The value of repeat kidney biopsy in quiescent Argentinian lupus nephritis patients. Lupus. 2014;23(8):840–847.

[12] Rovin BH, Solomons N, Pendergraft WF 3rd, Dooley MA, Tumlin J, Romero-Diaz J, Lysenko L, Navarra SV, Huizinga RB; AURA-LV Study Group. 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 Jan;95(1):219-231.

[13] Rovin BH, Teng YKO, Ginzler EM, Arriens C, Caster DJ, Romero-Diaz J, Gibson K, Kaplan J, Lisk L, Navarra S, Parikh SV, Randhawa S, Solomons N, Huizinga RB. Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet. 2021 May 29;397(10289):2070-2080. Erratum in: Lancet. 2021 May 29;397(10289):2048.

[14] Kodner C. Diagnosis and Management of Nephrotic Syndrome in Adults. Am Fam Physician. 2016 Mar 15;93(6):479-85.

[15] Academy of Managed Care Pharmacy (AMCP) dossier for LUPKYNIS (voclosporin) [online]. Aurinia Pharmaceuticals, Fort Washington, PA, 15 April 2021.

[16] Lee, Y.H., Song, G.G. A network meta-analysis of randomized controlled trials comparing the effectiveness and safety of voclosporin or tacrolimus plus mycophenolate mofetil as induction treatment for lupus nephritis. Z Rheumatol (2021). https://doi.org/10.1007/s00393-021-01087-z . *Published in English and German.*

[17] 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. *Am J Transplant.* 2011; 11:2675–2684

[18] Mayo PR, Ling SY, Huizinga RB, Freitag DG, Aspeslet LJ, Foster RT. Population PKPD of voclosporin in renal allograft patients. J Clin Pharmacol. 2014 May;54(5):537-45.

[19] Li Y, Palmisano M, Sun D, Zhou S. Pharmacokinetic Disposition Difference Between Cyclosporine and Voclosporin Drives Their Distinct Efficacy and Safety Profiles in Clinical Studies. Clin Pharmacol. 2020 Jul 1;12:83-96.

[20] Fanouriakis A, Kostopoulou M, Cheema K, et al. 2019 Update of the Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of lupus nephritis. Ann Rheum Dis. 2020 Jun;79(6):713-723.

[21] Hahn BH, McMahon MA, Wilkinson A, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res (Hoboken). 2012;64(6):797-808.

[22] Tang C, Godfrey T, Stawell R, Nikpour M. Hydroxychloroquine in lupus: emerging evidence supporting multiple beneficial effects. Intern Med J. 2012 Sep;42(9):968-78.

[23] Rovin BH, Caster DJ, Cattran DC, et al. Management and treatment of glomerular diseases (part 2): conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2019;95(2):281-295. KDIGO recommendations.

[24] Tamirou F, Houssiau FA. Management of Lupus Nephritis. J Clin Med. 2021 Feb 9;10(4):670.

[25] Fernandez Nieto M, Jayne DR. Con: The use of calcineurin inhibitors in the treatment of lupus nephritis. Nephrol Dial Transplant. 2016 Oct;31(10):1567-71.

[26] Chen X, Wang DD, Li ZP. Analysis of time course and dose effect of tacrolimus on proteinuria in lupus nephritis patients. J Clin Pharm Ther. 2021 Feb;46(1):106-113. doi: 10.1111/jcpt.13260. Epub 2020 Sep 25.

[27] Houssiau FA, Vasconcelos C, D'Cruz D, Sebastiani GD, Garrido Ed Ede R, Danieli MG, Abramovicz D, Blockmans D, Mathieu A, Direskeneli H, Galeazzi M, Gül A, Levy Y, Petera P, Popovic R, Petrovic R, Sinico RA, Cattaneo R, Font J, Depresseux G, Cosyns JP, Cervera R. Immunosuppressive therapy in lupus nephritis: the Euro-Lupus Nephritis Trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. Arthritis Rheum. 2002 Aug;46(8):2121-31.

[28] Gordon C, Jayne D, Pusey C, et al. European consensus statement on the terminology used in the management of lupus glomerulonephritis. Lupus. 2009;18(3):257–263.

[29] Kasitanon N, Boripatkosol P, Louthrenoo W. Response to combination of mycophenolate mofetil, cyclosporin A and corticosteroid treatment in lupus nephritis patients with persistent proteinuria. Int J Rheum Dis. 2018 Jan;21(1):200-207.

[30] 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. Clin J Am Soc Nephrol, 2006, 1(5):925-32.

[31] Austin HA 3rd, Illei GG, Braun MJ, Balow JE. Randomized, controlled trial of prednisone, cyclophosphamide, and cyclosporine in lupus membranous nephropathy. J Am Soc Nephrol. 2009 Apr;20(4):901-11.

[32] Ogawa H, Kameda H, Nagasawa H, Sekiguchi N, Takei H, Tsuzaka K, Amano K, Takeuchi T. Prospective study of low-dose cyclosporine A in patients with refractory lupus nephritis. Mod Rheumatol. 2007;17(2):92-7.

[33] Sheikholeslami M, Hajialilo M, Rasi Hashemi SS, Malek Mahdavi A, Gojazadeh M, Khabbazi A. Low dose cyclosporine A in the treatment of resistant proliferative lupus nephritis. Mod Rheumatol. 2018 May;28(3):523-529

[34] Falk, RJ, Dall'Era M, Appel GB. Clinical features and therapy of lupus membranous nephropathy. In: UpToDate, Glassock RJ, Rovin BH, Lam AQ (Eds), UpToDate, Waltham, MA, 2021. (Accessed 9 Jun 2021.)

[35] Liu Z, Zhang H, Liu Z, et al. Multitarget therapy for induction treatment of lupus nephritis: a randomized trial. Ann Intern Med. 2015 Jan 6;162(1):18-26. *Pivotal MC OL RCT in China for multitarget TAC regimen.*

[36] Bao H, Liu ZH, Xie HL, et al. Successful treatment of class V+IV lupus nephritis with multitarget therapy. J Am Soc Nephrol. 2008 Oct;19(10):2001-10.

[37] Tunnicliffe DJ, Palmer SC, Henderson L, et al. Immunosuppressive treatment for proliferative lupus nephritis. Cochrane Database Syst Rev. 2018 Jun 29;6(6):CD002922.

[38] Zhou J, Tao MJ, Jin LR, et al. Effectiveness and safety of common therapeutic drugs for refractory lupus nephritis: A network meta-analysis. Exp Ther Med. 2020 Jan;19(1):665-671.

[39] Li X, Ren H, Zhang Q, et al. Mycophenolate mofetil or tacrolimus compared with intravenous cyclophosphamide in the induction treatment for active lupus nephritis. Nephrol Dial Transplant. 2012 Apr;27(4):1467-72.

[40] Szeto CC, Kwan BC, Lai FM, et al. Tacrolimus for the treatment of systemic lupus erythematosus with pure class V nephritis. Rheumatology (Oxford). 2008 Nov;47(11):1678-81.

[41] Chen W, Tang X, Liu Q, et al. Short-term outcomes of induction therapy with tacrolimus versus cyclophosphamide for active lupus nephritis: A multicenter randomized clinical trial. Am J Kidney Dis. 2011 Feb;57(2):235-44.

[42] Wang S, Li X, Qu L, et al. Tacrolimus versus cyclophosphamide as treatment for diffuse proliferative or membranous lupus nephritis: a non-randomized prospective cohort study. Lupus. 2012 Aug;21(9):1025-35.

[43] 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. Ann Rheum Dis. 2016 Jan;75(1):30-6.
[44] Fei Y, Wu Q, Zhang W, et al. Low-dose tacrolimus in treating lupus nephritis refractory to cyclophosphamide: a prospective cohort study. Clin Exp Rheumatol. 2013 Jan-Feb;31(1):62-8.
[45] Facts & Comparisons. Facts & Comparisons eAnswers [online]. 2021. Available from Wolters Kluwer Health, Inc. Accessed 10 Jun 2021.
[46] Falk RJ, Dall'Era M, Appel GB. Lupus nephritis: Initial and subsequent therapy for focal or diffuse lupus nephritis. In: UpToDate, Glassock RJ, Rovin BH, Lam AQ, Ramirez Curtis M (Eds), UpToDate, Waltham, MA, 2021. (Accessed 3 Jun 2021.)
[47] Schur PH, Hahn BH. Epidemiology and pathogenesis of systemic lupus erythematosus. In: UpToDate, Pisetsky DS, Ramirez Curtis M (Eds). UpToDate, Waltham, MA, 2021. (Accessed 1 Jul 2021.)
[48] Sin FE, Isenberg D. An evaluation of voclosporin for the treatment of lupus nephritis. Expert Opin Pharmacother. 2018 Oct;19(14):1613-1621.
[49] Arnaud L, Tektonidou MG. Long-term outcomes in systemic lupus erythematosus: trends over time and major contributors. Rheumatology (Oxford). 2020 Dec 5;59(Suppl5):v29-v38.
[50] Mok CC. Therapeutic monitoring of the immuno-modulating drugs in systemic lupus erythematosus. Expert Rev Clin Immunol. 2017 Jan;13(1):35-41.