Lupus Nephritis: Maintenance Therapy for Lupus Nephritis—Do We Now Have a Plan?

Oliver Lenz,* Ahmed A. Waheed,† Abdur Baig,† Alexander Pop,† and Gabriel Contreras*

Summary
Lupus nephritis (LN) increases the morbidity and mortality of patients with SLE. This review compares the randomized, controlled trials that examined various maintenance regimens available to treat LN. Currently, mycophenolate mofetil (MMF) and azathioprine (AZA) are the most popular therapeutic agents used for long-term maintenance of LN. Long-term maintenance with MMF is recommended as the first choice after achieving remission with cyclophosphamide or MMF induction. MMF is effective in consolidating remission and preventing relapse and CKD in patients of diverse races and ethnicities. Long-term maintenance with AZA is the recommended second choice, especially when patients develop intolerance of or contraindications to MMF. Azathioprine is particularly effective in consolidating remission and preventing relapse and CKD in patients who receive an induction regimen of cyclophosphamide. To date, there are no data on how rapidly maintenance therapies can be withdrawn; however, it is recommended that the immunosuppressive therapy be maintained indefinitely, unless it is contraindicated, in patients at high risk for progression to CKD.

Introduction
Lupus nephritis (LN) is a common and serious complication of SLE. It occurs in 15%–60% of patients with SLE in the United States and Europe and in 45%–86% of patients in Japan (1–3). Severe forms of LN (focal proliferative GN [class III], diffuse proliferative GN [class IV], and membranous GN with or without proliferative features [classes V, V+III, and V+IV]), add to the burden of the already high morbidity and mortality of patients with SLE. Patients with severe forms of LN have a 47% cumulative probability of developing CKD or die during long-term follow-up (4). Fortunately, many advances in the treatment of SLE have been achieved over the past 50 years. Randomized, controlled trials (RCTs) of different therapeutic agents have significantly improved outcomes of SLE patients with severe forms of LN (Table 1). Recent clinical studies of sequential therapy for severe LN have clarified the therapeutic role of a variety of immunosuppressive agents (5). The concept of two phases of therapy—an intense induction phase and a less intense maintenance phase—is widely accepted with therapeutic agents used in transplantation and oncology. In sequential therapy, once a clinical remission has been induced with intense therapy, the goals of maintenance therapy are to consolidate the renal remission, to maintain remission or prevent renal relapse conducive to CKD, and to minimize drug toxicities.

During the maintenance phase of LN treatment, renal relapses, particularly the nephritic phase, are important predictors of poor renal outcomes, such as persistent doubling of serum creatinine and CKD. Predictors of relapse include a high activity index, increased proteinuria, cellular cast in the urine sediment, male sex, younger age, hypertension, delay in initiation of treatment, increased time to remission, and only a partial response to treatment (6–10).

In this article, we focus on the advances that have been made in the maintenance therapy for severe LN on the basis of completed RCTs.

Maintenance Therapeutic Agents for Severe Forms of LN: Corticosteroids, Cyclophosphamide, Azathioprine, Mycophenolate, and Calcineurin Inhibitors

From 1970 to 1996, landmark RCTs (11–15) conducted by the National Institutes of Health (NIH) compared regimens of different therapeutic agents plus corticosteroids with regimens of corticosteroids alone. Those studies established long-term cyclophosphamide (CY) as the most effective therapy; it was found to reduce the probabilities of CKD to 0%–25% and of dying to 11%–15% among SLE patients with severe LN. However, the success of prolonged therapy with CY came with the burden of adverse events. Use of CY for longer than 6 months caused substantial ovarian failure. Young women with SLE treated with long-term CY regimens had a high incidence of sustained amenorrhea ranging from 29% to 71%.

Recognizing that ovarian failure was substantial (13), the NIH group compared the efficacy and safety of short-term intravenous CY (IVCY) induction using only six monthly pulses of IVCY with corticosteroids, followed by maintenance with corticosteroids alone, with those of a long-term IVCY regimen involving the same 6-month induction regimen followed by...
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<th>Author</th>
<th>Class of Nephritis (n)</th>
<th>Creatinine (mg/dl)</th>
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<td>Houssiau et al., 2002 (18)</td>
<td>Class III: 21 Class IV: 62 Class Vc/Vd: 7</td>
<td></td>
<td>High-dose IVCY: 1.21±0.76 Low-dose IVCY: 1.09±0.54</td>
<td>Multicenter, prospective clinical trial (Euro-Lupus Nephritis Trial)</td>
<td>41.3</td>
<td>6/84, 31</td>
<td>Induction: Group 1: High-dose IVCY (500 mg/m² BSA titrated to WBC count nadir; six monthly and two quarterly pulses); group 2: low-dose IVCY (six fortnightly pulses of 500 mg); both groups received corticosteroids Maintenance: AZA (2 mg/kg per day) in both groups and low-dose corticosteroids</td>
<td>Efficacy outcome (high-dose IVCY followed by AZA and low-dose IVCY followed by AZA): Remission consolidation: 70% and 85% Renal flare: 29% and 27% ESRD: 4.4% and 2.2% Safety outcomes (high-dose IVCY followed by AZA and low-dose IVCY followed by AZA): Severe infections: 22% and 11% Amenorrhea: 2% in both groups Mortality: 0% and 4.5%</td>
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<td>Contreas et al., 2004 (20)</td>
<td>Class III: 12 Class IV: 46 Class Vb: 1</td>
<td>Before maintenance therapy IVCY: 0.97±0.5 AZA: 0.96±0.5 MMF: 1.16±0.7</td>
<td>Single-center, randomized, open-label, controlled trial</td>
<td>83</td>
<td>4/55, 32.7</td>
<td>Induction: Maximum, 7 monthly boluses of IVCY (500–1000 mg/m² BSA) and corticosteroids Maintenance: Group 1: Quarterly IVCY (500–1000 mg/m²); group 2: oral AZA (1–3 mg/kg per day); group 3: MMF (0.5–3 g/d in divided dose); all groups for 1–3 years and with low-dose corticosteroids</td>
<td>Efficacy outcome (IVCY, AZA, and MMF): Relapse: 40%, 31.5%, and 19% CKD or mortality: 35%, 5.2%, and 10% CKD: 15%, 5.2%, and 5% Safety outcomes (IVCY, AZA, and MMF): Infections: 77%, 29%, and 32% Amenorrhea: 32%, 8%, and 6% Mortality: 0%, 0%, and 5%</td>
<td>Short-term therapy with IVCY followed by maintenance therapy with MMF or AZA appears more efficacious and safer than long-term therapy with IVCY</td>
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<td>Chan <em>et al.</em>, 2005</td>
<td>Class IV (IV-S or IV-G): 62</td>
<td>MMF group: 1.27±0.74 CY-AZA group: 1.28±0.53</td>
<td>Open-label, randomized, controlled trial</td>
<td>63</td>
<td>10/52, 39.9</td>
<td>Group 1: Induction with MMF (1 g twice daily) for 6 mo, then MMF (0.5–0.75 g twice daily) for another 6 mo and corticosteroids, maintenance with MMF or AZA (1–1.5 mg/kg per day) and low-dose corticosteroids for &gt;2–3 yr; group 2: induction with CY (2.5 mg/kg per day) for 6 mo, followed by AZA (initially 1.5–2 mg/kg per day; after 6 mo, 1–1.5 mg/kg per day) for another 6 mo and corticosteroids, maintenance with AZA and low-dose corticosteroids</td>
<td>Efficacy outcome (MMF and CY-AZA): Remission consolidation: 96.8% and 98.9% Relapse: 34.3% and 30% Progressive renal impairment/ESRD: 12.5% and 10% Safety outcomes (MMF and CY-AZA): Infections: 12.5% and 40%&lt;sup&gt;a&lt;/sup&gt; Amenorrhea: 3.5% and 36%&lt;sup&gt;b&lt;/sup&gt; Mortality: 0% and 6.5%</td>
<td>MMF and prednisolone constitute an effective continuous induction-maintenance treatment of diffuse proliferative lupus nephritis in Chinese patients</td>
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<td>Grootscholten <em>et al.</em>, 2006</td>
<td>Class III or Vc: 8 Class IV or Vd: 79</td>
<td>CY: 1.26 (0.97–1.73) AZA: 1.23 (0.93–1.82)</td>
<td>Open-label, randomized, controlled trial (Dutch Lupus Nephritis study)</td>
<td>67</td>
<td>12/75, 31.5</td>
<td>Induction: Group 1: IVCY pulses (750 mg/m$^2$, six monthly pulses, then seven quarterly pulses in 2 yr) and corticosteroids; group 2: AZA (2 mg/kg per day in 2 yr) combined with IV pulses of methylprednisolone (1000-mg cycles of 3 d at entry, 2 wk, and 6 wk) and oral corticosteroids; maintenance with AZA and low-dose corticosteroids</td>
<td>Efficacy outcome (IVCY-AZA and AZA): Nonsustained doubling of creatinine: 4% and 16%&lt;sup&gt;a&lt;/sup&gt; Relapse: 4% and 27%&lt;sup&gt;a&lt;/sup&gt; ESRD: 0% and 27% Safety outcomes (IVCY-AZA and AZA): Infections in first 2 yr: 18 versus 37 events/100 patient-years&lt;sup&gt;a&lt;/sup&gt; Herpes zoster virus 6% and 32%&lt;sup&gt;a&lt;/sup&gt; Mortality: 4% and 8.1%</td>
<td>CY for 24 mo followed by AZA is superior to continuous AZA induction-maintenance with regard to renal relapses and herpes zoster virus</td>
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<td>Moroni et al., 2006 (25)</td>
<td>Class IV: 60 Class Vc or Vd: 9</td>
<td>CY: 0.9±0.23AZA: 0.9±0.29</td>
<td>Multicenter, randomized, prospective study</td>
<td>48</td>
<td>7/62, 31.5</td>
<td>Induction: CY (1–2 mg/kg per day) for 3 mo and corticosteroids Maintenance: Group 1: CYS (initial dosage, 4 mg/kg per day); group 2: AZA (initial dosage, 2 mg/kg per day); both groups for 2 yr and with low-dose corticosteroids</td>
<td>Efficacy outcome (CYS and AZA): Relapse: 19.4% and 24.2% Treatment discontinued: 13.8% and 12.1% ESRD: 0% in both groups Quality outcomes (CYS and AZA): Leukopenia: 6% and 17%; Infections: 11% and 23%; Hypertension: 22.2% and 15.2%; Arthralgias: 21% and 5%; Mortality: 0% in both groups</td>
<td>Both regimens considered efficacious; some difference in side effects</td>
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<td>Austin et al., 2009 (27)</td>
<td>Class V: 42</td>
<td>GFR, ml/min per 1.73 m² Prednisone: 80 (32–112) IVCY: 80 (61–112) Cyclosporine: 89 (68–189)</td>
<td>Prospective, randomized clinical trial</td>
<td>60</td>
<td>7/35, 40</td>
<td>Group 1: High-dose alternate-day oral prednisone (40 mg/m² of BSA) every other day for 8 wk, followed by gradual tapering (10 mg/m² of BSA) for 12 mo; group 2: IVCY (six doses, 500–1000 mg/m² BSA) every other month; group 3: CYS (200 mg/m² BSA per day, equally divided doses every 12 h) for 12 mo</td>
<td>Efficacy outcome (prednisone, IVCY, and CYS): Nephrotic relapse after discontinuation of therapy: 60% in CYS and 20% in IVCY groups (not reported in the prednisone group) Safety outcomes (prednisone, IVCY, and CYS): Infections: 26.7%, 66.7%, and 58.3%; Amenorrhea: 0%, 25%, and 0%</td>
<td>Regimens containing CYS or IVCY are each more effective than prednisone alone among patients with lupus membranous nephropathy</td>
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<tr>
<td>Houssiau et al., 2010 (23)</td>
<td>Class III: 33</td>
<td>1.02±0.47</td>
<td>Multicenter, randomized, prospective trial</td>
<td>48</td>
<td>9/96, 33</td>
<td>Induction: Low-dose IVCY (six fortnightly pulses of 500 mg) with corticosteroids Maintenance: Group 1: AZA (2 mg/kg per day); Group 2: MMF (1 g twice daily); both group for ≥36 mo and with low-dose corticosteroids</td>
<td>Efficacy outcome (AZA and MMF): Remission consolidation: 90.4% and 88.7%; Renal flare: 25% and 19%; Doubling of creatinine: 7.7% and 5.7%; ESRD: 1.9% and 1.8%; Systemic relapse: 7.7% and 5.7%; Safety outcomes (AZA and MMF): Cytopenias: 23% and 3.8%; All infections: 48% and 60%; Transient amenorrhea: 1.9% and 3.7%; Mortality: 0% and 3.7%</td>
<td>Fewer renal flares were observed with MMF (but difference was not statistically significant)</td>
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<td>Dooley et al., 2011 (24)</td>
<td>Class III or III V: 29</td>
<td>MMF: 0.82±0.24 AZA: 0.90±0.38</td>
<td>Prospective, randomized, double-blind study (Aspreva Lupus Management Study)</td>
<td>36</td>
<td>32/195, 31.4</td>
<td>Induction: Oral MMF (1.5 g twice daily) or IVCY (monthly 500–1000 mg/m² BSA) for 6 mo and corticosteroids Maintenance: Group 1: Oral MMF (1 g twice daily); group 2: AZA (2 mg/kg per day); both groups for 36 mo and with low-dose corticosteroids</td>
<td>Efficacy outcome (MMF and AZA): Complete remission consolidation: 62.1% and 59.5% Treatment failure: 16.4% and 32.4% Renal flare: 12.9% and 23.9% Use of rescue therapy for renal relapse: 7.8% and 17.1% Doubling of creatinine: 0.9% and 4.5% ESRD: 0% and 2.7% Safety outcomes (MMF and AZA): Adverse events leading to withdrawal: 25.2% and 39.6% Serious adverse events: 23.5% and 33.3% All infections: 79.1% and 78.4% Mortality: 0% and 0.9%</td>
<td>MMF superior to AZA in maintaining renal response to treatment and in preventing relapse in patients who had responded to induction therapy</td>
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Creatinine is reported as mean with SD or median with range. GFR is reported as median with range. Unless otherwise noted, *P* > 0.05. *P* values are reported per publications and their applied statistical methods. Results extracted from publications are reported preferentially as proportions of the crude incidence and, when missing, as incidence rate or as cumulative incidence derived from Kaplan-Meier product-limit survival distributions. M/F, male/female; IVCY, intravenous cyclophosphamide; BSA, body surface area; WBC, white blood cell; AZA, azathioprine; MMF, mycophenolate mofetil; CY, oral cyclophosphamide; IV, intravenous; CYS, cyclosporine.

*P* < 0.05.  
*P* < 0.01.
approximately 12 more pulses of quarterly IVCY with corticosteroids as maintenance therapy. Although the incidence of sustained amenorrhea was significantly lower in the short-term IVCY group than in the long-term IVCY group (17% versus 64%), patients in the short-term IVCY group had a significantly higher probability of renal relapse when they were not treated with maintenance immunosuppression other than corticosteroids (60% versus 13% in long-term IVCY group). Earlier studies from the Mayo Clinic and the Lupus Nephritis Collaborative Study Group also showed that the early advantages of short-term oral CY induction disappeared over time when corticosteroids alone were used as maintenance therapy (16,17). Therefore, maintenance with corticosteroids alone cannot be recommended for a patient with SLE who just achieved remission of severe LN.

During the past two decades, landmark RCTs have compared sequential regimens of immunosuppressive agents (18–24). Azathioprine (AZA) is the first therapeutic agent tested for long-term maintenance in sequential regimens for severe LN. Houssiau et al. (18), in the Euro Lupus Nephritis Trial (ELNT), which enrolled patients with SLE who were of predominantly white ancestry, demonstrated that AZA maintenance was efficacious and safe; it consolidated renal remission (70%±85%), prevented renal relapses (27%–29%) and CKD (7%–9%), and minimized drug toxicity (7% amenorrhea, 4%–5% severe infections) after induction with IVCY at high dose (six monthly CY pulses and two quarterly pulses at a dose of 0.5 g/m²; n=46) or low dose (CY fixed dose of 0.5 g every 2 weeks for six pulses; n=44) with corticosteroids. Only two patients (5%) died, both in the low-dose IVCY group. In another RCT among primarily white patients with severe LN, Grootscholten et al. (19) demonstrated that long-term maintenance with AZA was more efficacious and safe in preventing nonsustained doubling of serum creatinine (4% versus 16%), renal relapses (4% versus 27%), and herpes zoster infections (6% versus 32%) after induction with IVCY (consisting of six monthly pulses and seven quarterly pulses at a dose of 0.75 g/m²; n=50) than induction with AZA (2 mg/kg per day; n=37) plus IV methylprednisolone (3-day 1000-mg cycles at entry, 2 weeks, and 6 weeks). Other efficacy and safety outcomes (including mortality, 4% and 8%) were similar between the two regimens. In both trials, patient mortality and CKD rates were similar for all sequential regimens. However, the relapse rate of 4% was substantially lower when long-term maintenance with AZA was started after 24 months of IVCY pulses compared with AZA started after 3 and 12 months of IVCY pulses in Grootscholten and colleagues’ trial (19) and the ELNT (18), respectively.

The University of Miami single-center study (20) compared the long-term efficacy and safety of three maintenance immunosuppressive agents—quarterly IVCY (0.5–1 g/m²; n=20), mycophenolate mofetil (MMF) (0.5–3 g daily; n=20), and AZA (1–3 mg/kg per day; n=19)—for severe LN in 59 patients with SLE who had received a similar short-term IVCY plus corticosteroid induction before randomization. It included more Hispanic-American (49%) and African-American (46%) than white (5%) patients. During the long-term follow-up of 72 months, the probability of developing the primary composite endpoint of death or CKD (sustained doubling of serum creatinine or ESRD) was lower in the MMF (10%) and AZA (5.3%) groups than in the IVCY group (35%). The probability of relapse was lower in the MMF group (15%) than in the AZA (32%) and IVCY (40%) groups. Adverse events, such as hospitalization (1 and 1 versus 10 hospital-day per patient-year of follow-up), amenorrhea (6% and 8% versus 32%), and severe infections (2% and 2% versus 25%), were significantly less common in the MMF and AZA groups than the IVCY group. The study demonstrated for the first time that maintenance therapy with MMF or AZA after short-term IVCY induction in sequential regimens is an efficacious, safe alternative therapy in high-risk patients with SLE, in whom long-term IVCY was associated with poor outcomes. It is important to note that the study included patients of predominantly Hispanic and African ancestries, as opposed to the predominantly white patients in prior trials (11–16,18,19).

In Asian patients with diffuse proliferative LN, Chan et al. (21,22) conducted landmark studies that showed similar efficacy between a regimen of oral MMF and sequential oral CY followed by AZA. The long-term 5-year follow-up demonstrated that prolonged MMF induction—maintenance (n=32) and sequential CY-AZA induction—maintenance (n=30) therapies were similar in consolidating remission (complete and partial remission, 96.8%–98.9%) and preventing relapse (30%–34%) and CKD (13% in both groups). For maintenance therapy with MMF versus AZA, there was a significantly lower incidence of leukopenia (0% versus 26%) and infections (13% versus 40%) (22). Only two patients died (7%) in the sequential CY-AZA group. These studies first demonstrated the efficacy and safety of MMF for the treatment of proliferative LN in Asian populations.

Currently, MMF and AZA are the most popular therapeutic agents used for long-term maintenance of LN. The studies of Chan et al. (22) and the University of Miami (20) demonstrated the efficacy and safety of MMF and AZA. However, the studies were small and lacked sufficient power to show significant differences between MMF and AZA as long-term maintenance therapies for LN. Only two recently published landmark RCTs (23,24) had enough power and long-term follow-up to assess the superiority of one therapeutic agent over another.

In the MAINTAIN Nephritis Trial (23), Houssiau et al. conducted a superiority RCT that compared MMF with AZA for long-term maintenance of LN. A total of 105 patients initially received intravenous pulses of methylprednisolone (1000 mg daily for 3 days at entry), followed by oral glucocorticoids and six fortnightly IVCY doses (fixed dose of 0.5 g every 2 weeks for six pulses). As part of maintenance therapy, patients were randomly assigned to start therapy at week 12 with AZA (n=52; target dose, 2 mg/kg per day) or MMF (n=53; target dose, 2 g/d). Patients were not required to achieve remission in order to proceed to the maintenance phase. Thirteen (25%) AZA-treated and 10 (19%) MMF-treated patients had a renal relapse, the primary end point of the trial. There was no statistical difference between the two maintenance groups in comparing the primary and other secondary end points, such as consolidation of renal remission (90.4% versus 88.7%), severe systemic relapse (7.7% versus
5.7%), doubling of serum creatinine (7.7% versus 5.7%), ESRD (1.9% versus 1.8%), and death (0% versus 3.8%). Adverse events did not differ between the groups except for a significant difference in the incidence of cytopenias, which were more frequent in the AZA group (25% versus 3.8% in the MMF group). The observed difference in renal relapse rates was small: only 6%, favoring MMF. The study size had a power of 80% to detect an expected 20% greater difference in the rate of renal relapse (35% in the AZA and 10% in the MMF groups) with a probability level of 0.05, and it is unclear whether an increase in the number of enrolled patients would have changed this difference. Consequently, the investigators concluded that as maintenance therapy, MMF was not superior to AZA after low-dose IVCY induction for European patients.

In the recently published results of the Aspreva Lupus Management Study (ALMS), Dooley et al. concluded that MMF is superior to AZA as a long-term maintenance therapy (24). Two hundred twenty-seven patients with SLE were randomly assigned to receive MMF (n=116; 2 g/d) or AZA (n=111; 2 mg/kg per day) maintenance in a double-blinded, double-dummy treatment strategy after 6 months of induction with IVCY or MMF. Achievement of remission was required to proceed into the maintenance phase. ALMS included patients of diverse races (43.6% white, 33.5% Asian, 10.1% African, and 12.8% others) and ethnicities (51.1% non-Hispanic and 48.9% Hispanic). The primary composite end point was time to treatment failure: death, ESRD, doubling of serum creatinine, renal relapse, or use of rescue therapy for LN. The study had a power of >80% to detect an expected difference of 17.5% in the rate of treatment failure (37.5% in the AZA and 20% in the MMF groups) with a probability level of 0.05. Secondary end points included the time to the individual components of treatment failure, suspected renal relapse, complete renal remission, combined renal and extrarenal remission, immunologic variables, and adverse events. The use of MMF was found to be superior to AZA with respect to treatment failure (16.4% versus 32.4%), renal relapse (12.9% versus 23.9%), and use of rescue therapy (7.8% versus 17.1%). Other outcomes showed a nonsignificant but numerically beneficial effect of MMF versus AZA: doubling of the serum creatinine level (0.9% versus 4.5%), ESRD (0% versus 2.7%), and death (0% versus 0.9%). In subgroup analyses, statistical significance was not reached in interaction tests, but MMF consistently showed a numeric advantage over AZA in reducing the risk for treatment failure, regardless of induction therapy, race, and geographic region. Stratified by induction therapy, the crude incidence rates of treatment failure for MMF compared with AZA were 11.1% and 28% after IVCY induction and 20.9% and 36.2% after induction with MMF, respectively. A lower rate of serious adverse events was noted in the MMF group (23.5% versus 33.3%). The rate of withdrawal due to adverse events was also lower in the MMF group (25.2% versus 39.6%).

Some important similarities and differences between ALMS and the MAINTAIN study (23,24) are worth mentioning here. The study designs of the two studies were different. Patients randomly assigned to the maintenance phase in ALMS had responded to one of two induction regimens at 24 weeks, excluding nonresponders, and consequently represent a selected population. In the MAINTAIN study, all patients were randomly assigned at baseline and received a sequential regimen with an initial 12 weeks of IVCY followed by allocation to AZA or MMF in continuous induction and maintenance regimens, including nonresponders with responders, without a clear ascertainment of the time of transition from induction to maintenance in responders. Both studies had a similar hypothesis: that MMF is superior to AZA. ALMS used a primary composite end point that included renal relapse, the single primary outcome used in the MAINTAIN study. ALMS included more patients: It is more than double the size of the MAINTAIN study. These two differences provided ALMS sufficient power to show that MMF is significantly superior to AZA in preventing treatment failure. Additionally, in ALMS, MMF was also significantly superior to AZA, preventing renal relapse. This result was in part related to the clinically important observed difference of 11%. The difference cannot be attributed to the adjudication of outcomes, which were reviewed by the end point committee blinded to the maintenance therapy. In both studies, the observed incidence of renal relapse was consistently similar to that with AZA maintenance (23.9% and 25%); however, the observed rate of renal relapse with MMF maintenance was lower in ALMS (12.9%) than in the MAINTAIN study (19%). The patients included in the MAINTAIN study were predominantly white, whereas ALMS patients were more racially diverse, with a large inclusion of Hispanic patients. This could have accounted for the difference in relapse rate in the MMF groups of both studies.

Calcineurin inhibitor regimens have also been proposed as reasonable alternative maintenance therapies for LN. However, the risk for relapse seems high with their short-term use, particularly in high-risk patients. The risk for CKD from long-term exposure to calcineurin inhibitors is still not known because clinical trials limited the exposure of those drugs to a maximum of 24 months of active therapy. Moroni et al. (25) in a maintenance RCT compared cyclosporine (n=36) with AZA (n=33) for 24 months in predominantly white patients with SLE who had diffuse proliferative LN. Relapses were similar in the two groups (19.4% and 24.2%). At the last follow-up, creatinine clearance and BP values did not change significantly from baseline in either group. The incidence of leukopenia (17% versus 6%) and all infections (23% versus 11%) were higher in the AZA than the cyclosporine group; however, the incidence rates of arthralgias (21% versus 5%) and hypertension (22.2% versus 15.2%) were higher in the cyclosporine than the AZA group.

In another RCT, Chen et al. (26) compared tacrolimus with AZA maintenance. Seventy Chinese patients who achieved remission of LN were randomly assigned to tacrolimus plus prednisone (n=34) or AZA plus prednisone (n=36) for 6 months. The tacrolimus dose was titrated to achieve a trough blood concentration of 4–6 ng/ml, and the dosage of AZA was 2 mg/kg per day. In the short-term follow-up, relapses were also similar in the two groups (0% and 5.6%). Leukopenia was significantly less frequent in the tacrolimus group than the AZA group (9% versus 47%).

Austin et al. (27) conducted an RCT to compare cyclosporine (n=12), IVCY (n=15), and prednisone (n=15) for the treatment of membranous LN. During the 24-month
active therapy phase, both cyclosporine and IVCY were more effective than prednisone in maintaining remission. However, nephrotic syndrome relapsed significantly more often after completion of cyclosporine (60%) than after IVCY (20%) during an extended cumulative follow-up of 72 months. It is important to note that in that study more African-American than white patients were randomly assigned to the cyclosporine group.

Conclusion
Currently available clinical trials propound sequential therapy as an effective and safer alternative for treating severe LN in patients of white, Asian, African, or Hispanic ancestry (18–26). We have seen a comforting decline in CKD (7% or less) and mortality (10% or less) with the use of sequential therapies in the past two decades. Still, the relapse range varies between 4% and 40% in studies with long-term follow-up. There are several therapeutic options for long-term maintenance of LN. We recommend long-term maintenance with MMF as the first choice after achieving remission with CY or MMF induction. In ALMS, MMF was superior to AZA with respect to treatment failure and renal relapse. In stratified analyses, the treatment failure rate was the lowest—11.1%—in the sequential therapy group receiving IVCY induction followed by MMF maintenance. Additionally, MMF is an effective induction therapeutic agent that can consolidate complete remission, which was achieved in 62% of patients with SLE enrolled in the MMF group. Long-term maintenance with AZA is our second choice, particularly when patients develop intolerance of or contraindications to the use of MMF. In addition, because it costs less than MMF, AZA can be propelled as an initial choice for maintenance of LN. Long-term maintenance with AZA is effective in consolidating remission and preventing relapse and CKD, particularly in patients who initially receive induction with CY. To date, there are no data to inform the physician on how quickly maintenance therapies can be withdrawn; however, we recommend that the immunosuppressive therapy be maintained indefinitely, unless contraindicated, in patients with risk factors for progression to CKD, such as African ancestry, Hispanic ethnicity, young age, biopsy showing crescents in the glomeruli with or without high chronicity index, lack of complete remission with persistently elevated serum creatinine levels or significant proteinuria, persistently elevated antiphospholipid antibody levels, persistently low levels of complement component C3, and frequent relapses (28).

Disclosures
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References
1. Yokoyama H, Okuyama H, Yamaya H, Suzuki K, Osato T, Akamari R, Inoue M, Horiuchi G, Hamada Y, Suzuki N, Yasuda Y, Fujita T: Nephrotic syndrome relapsed significantly more often after completion of cyclosporine (60%) than after IVCY (20%) during an extended cumulative follow-up of 72 months. It is important to note that in that study African-American than white patients were randomly assigned to the cyclosporine group.

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