Impact of the ALMS and MAINTAIN trials on the management of lupus nephritis

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ABSTRACT

Current treatment of lupus nephritis consists of both induction and maintenance therapy, with the latter being designed to consolidate remissions and prevent relapses. Long-term maintenance treatment with intravenous cyclophosphamide was effective but associated with considerable toxicity. A small but well-designed controlled trial found that for post-induction maintenance therapy, both oral mycophenolate mofetil (MMF) and oral azathioprine were superior in efficacy and had reduced toxicity than a regimen of continued every third month intravenous cyclophosphamide. Although these oral agents were rapidly accepted and utilized as maintenance medications, their usage was based on scant evidence and there were no comparisons between the two. Recently, two relatively large, randomized, well-controlled, multicenter trials dealing with maintenance therapy for severe lupus nephritis have been completed. The Aspreva Lupus Management Study (ALMS) maintenance and MAINTAIN nephritis trials provide important information regarding the comparative efficacy and safety of MMF and azathioprine as maintenance therapies, as well as information on the effect of dosage and duration of treatment with these agents.

INTRODUCTION

Lupus nephritis is a common complication of systemic lupus erythematosus and increases both morbidity and mortality in the lupus population. While the standard induction therapy in the form of cyclophosphamide or mycophenolate mofetil (MMF) is effective in attaining clinical remission, relapses following initial remission have been historically common, occurring in up to 50% of patients with proliferative lupus nephritis following reduction in or cessation of immunosuppression [1–6]. Relapses are associated with an increase in morbidity as well as a greater risk of progressive chronic kidney disease [7–9]. It has been proposed that maintenance immunosuppression will prevent relapses and flares of the disease and lead to improved survival rates, while avoiding the toxicity of repeated cycles of high-dose immunosuppressive induction regimens. In the past, maintenance treatment often consisted of repeated doses of intravenous cyclophosphamide and was associated with considerable mortality and morbidity. Unfortunately, until recently, few studies have dealt specifically with maintenance regimens.

In the past 2 years, two landmark randomized trials of maintenance therapy in lupus nephritis have been completed: the MAINTAIN nephritis trial [10] and the maintenance phase of the Aspreva Lupus Management Study (ALMS) [11]. Both trials compared azathioprine (AZA) with MMF in patients diagnosed with proliferative lupus nephritis who had undergone successful induction therapy. Publication of the results represents a major progress in establishing a high-quality evidence base to inform therapeutic strategies for this disease. In this review, we will examine the impact of these two trials on current strategies for the maintenance therapy of lupus nephritis.
cyclophosphamide enhanced renal survival in patients with proliferative lupus nephritis. Unfortunately, such regimens have considerable toxicity in terms of infertility, risk of infections and the long-term risk of bladder and other tumors [12–15].

In 2004, Contreras et al. [16] conducted a randomized controlled trial evaluating the safety and efficacy of two oral maintenance regimens—MMF and AZA—when compared with maintenance intravenous cyclophosphamide (IVC). Fifty-nine predominantly Black and Hispanic female patients with Class III and IV lupus nephritis [a single subject had World Health Organization (WHO) Class Vb] were included in the study, performed at a single academic center. Lupus nephritis was severe in most patients: the mean baseline creatinine was 1.6 mg/dL (141.4 µmol/L), most had active urinary sediments, and 64% had nephrotic-range proteinuria. All patients received induction therapy, which consisted of up to seven monthly boluses of IVC (0.5–1 g/m2) and corticosteroids. The patients were subsequently randomized to receive one of the three maintenance therapy regimens: IVC (0.5–1.0 g/m2 every 3 months), oral AZA (1–3 mg/kg daily) or oral MMF (500–3000 mg daily as tolerated). All three groups received oral prednisone (up to 0.5 mg/kg/day) as part of their maintenance immunosuppression. Patients treated with AZA had a significantly higher survival rate than those in the IVC group (P = 0.02). Although it did not reach statistical significance, there was a strong suggestion of better survival in the MMF group when compared with IVC (P = 0.11), and indeed the MMF and AZA groups were statistically indistinct. When using the composite endpoint of death or chronic renal failure, both the AZA and MMF groups had significantly better event-free survival rates than the IVC group. MMF also protected against renal relapse better than IVC. Perhaps most importantly, the improved clinical outcomes of AZA and MMF over IVC were complemented by a marked reduction of adverse effects, including the crucially important categories of hospitalization days, amenorrhea and total and major infections.

Overall, this important trial demonstrated the efficacy of oral maintenance therapies in the treatment of lupus nephritis, with better safety profiles compared with cyclophosphamide. For many clinicians, this study quickly relegated IVC to a role in induction therapy of severe lupus nephritis. However, it left a number of important questions unanswered. What is the dose of the oral agents necessary to prevent relapse or flares? How long is maintenance therapy to be continued? Which of the oral agents used is superior in efficacy? Which gives fewer side effects? These questions set the stage for larger and more definitive trials to compare MMF and AZA in the maintenance of lupus nephritis.

The ALMS Trial

The Aspreva Lupus Management Study [11, 17], one of the largest trials ever conducted in lupus nephritis, was a prospective randomized trial performed at 88 centers across the globe which utilized a two-phase design to test both induction strategies and maintenance strategies. The open-label induction phase tested whether MMF was superior to IVC for induction of lupus nephritis, whereas the subsequent maintenance phase compared MMF with oral AZA in a double-blind fashion. In the induction phase of the trial [17], 370 patients with International Society of Nephrology/Renal Pathology Society Class III, IV or V lupus nephritis were randomized to receive 24 weeks of treatment with either IVC or MMF; both groups received corticosteroids. The primary endpoint was renal response at 6 months. The response was defined as a decrease in the urine protein/creatinine ratio to <3 g/g (339 mg/mmol) in patients with baseline nephrotic-range proteinuria, or by >50% in patients with baseline sub-nephrotic proteinuria, as well as stabilization or improvement of serum creatinine (SCr) at 24 weeks. The renal response was achieved in 56.2% of the MMF group and 53% of the IVC group (P = 0.58). There were similar rates of serious adverse events and mortality in both groups. Thus, in the induction phase of the ALMS study, MMF showed equivalency to IVC for the therapy of severe lupus nephritis. As the second large trial showing no superiority of the alkylating agent in the treatment of lupus nephritis, it established MMF as a potential first-line therapy for many patients with the disease.

In the recently published maintenance phase of the ALMS trial [11], patients who had achieved response or remission with induction therapy (N = 227) were re-randomized to 3 years of treatment with either MMF (2 g/day) or AZA (2 mg/kg/day). Up to 10 mg/day of prednisone was administered at the discretion of the investigator. Randomization was stratified by race, biopsy class and induction therapy to ensure approximately equal number of patients in each arm who had been previously treated with MMF or cyclophosphamide. The treatment groups were well balanced in terms of both demographic and clinical parameters. The mean SCr was 0.8–0.9 mg/dL (70.7–79.6 µmol/L) and the mean 24-h urinary protein excretion was just <1 g/day in both groups. The primary endpoint was time to treatment failure, defined as renal flare (proteinuric or nephritic), sustained doubling of SCr, initiation of rescue therapy, end-stage renal disease (ESRD) or death. MMF was significantly superior to AZA with respect to this primary endpoint (hazard ratio, 0.44; 95% confidence interval (CI), 0.25–0.77; P = 0.003), and the superiority was valid regardless of the initial induction therapy (MMF or IVC), racial background or geographic region. The overall treatment failure rate in the MMF group was half that observed in the AZA group: 16.4% versus 32.4%, respectively. MMF was also significantly superior to AZA with regard to time to renal flare (hazard ratio, 0.50; 95% CI 0.26–0.93; P = 0.03) and time to rescue therapy (hazard ratio, 0.39; 95% CI 0.18–0.87; P = 0.02). The rates of renal flare were 12.9% in the MMF group and 23.4% in the AZA group; the rates of rescue were 7.8% with MMF and 17.1% with AZA. The incidence of adverse events—infection being the most common—was similar in the two groups, but the proportion of patients with adverse events leading to withdrawal was notably higher in the AZA group (39.6% compared with 25.2% in the MMF group).

In summary, the maintenance phase of the ALMS trial demonstrated that, regardless of induction therapy, MMF was superior to AZA in maintaining the renal response and...
preventing relapse of proliferative lupus nephritis. The superiority of MMF was irrespective of race, gender or region. The pattern and frequency of adverse events were consistent with what has been previously reported for AZA and MMF, with more withdrawals due to adverse events in the AZA group. Overall, the maintenance phase of the ALMS trial demonstrated a superior clinical benefit from MMF over AZA as maintenance therapy for lupus nephritis.

**THE MAINTAIN NEPHRITIS TRIAL**

The MAINTAIN nephritis trial [10], published in 2010, also addressed the question of optimal maintenance therapy in proliferative lupus nephritis. The core group of investigators of the MAINTAIN trial had previously conducted the Euro-Lupus nephritis trial [18], which demonstrated that corticosteroids plus low-dose IVC (500 mg every 2 weeks for six doses) was as effective as corticosteroids plus high-dose IVC for induction therapy in a European population. Long-term follow-up data for the Euro-Lupus cohort confirmed that the good clinical outcomes seen with low-dose IVC in the short-term were still evident at 10 years, with only 5% of the low-dose group and 9% of the high-dose group developing ESRD [19]; this undoubtedly was also reflective of the relatively good prognostic features of the baseline cohort. Importantly, AZA was the medication used to maintain remission for all subjects in the Euro-Lupus trial.

In light of the emerging data demonstrating MMF’s efficacy in lupus nephritis, the MAINTAIN nephritis trial was designed to test the superiority of MMF over AZA for maintenance therapy of lupus nephritis on the background of the Euro-Lupus induction regimen. This was an investigator-initiated trial performed at 27 European centers. A total of 105 patients with WHO Class III, IV or Vc-d lupus nephritis were randomized to two treatment groups. Both groups received identical induction therapy with IVC (500 mg every 2 weeks for six doses) after which one group received MMF (target dose 2 g/day) and the other AZA (target dose 2 mg/kg/day), regardless of response to induction therapy. Corticosteroids were administered on a defined taper. Only patients with at least 0.5 g/day of proteinuria were included in the study, and patients were excluded if they had received MMF, AZA, cyclophosphamide or cyclosporine A within the past year. The primary endpoint was time to renal flare, defined as either recurrence or development of nephrotic syndrome, renal impairment (a 33% or greater increase in SCR directly attributed to lupus within a one-month period) or a 3-fold increase in proteinuria within a 3-month period in patients with baseline proteinuria of less than 1 g/day.

At a mean follow-up time of 48 months, there was no significant difference between the AZA and MMF groups with respect to the primary outcome. Renal flare occurred in 19% of the MMF group, compared with 25% of the AZA group (hazard ratio 0.75, 95% CI 0.33–1.71, P = 0.49). There were also no significant differences in the number of patients achieving renal remission or withdrawing from glucocorticoids. Only one patient from each group developed ESRD.

Adverse events were well balanced between the groups with the exception of hematological cytopenias, which were more frequent in the AZA group. Overall adherence to the study protocol was excellent for this type of trial, with <25% dropout over 5 years of follow-up.

Further supporting the equal efficacy of MMF and AZA in the MAINTAIN nephritis trial were the separately published results of kidney biopsies performed in 30 patients (16 AZA and 14 MMF) at 2 years of follow-up. In both groups, the activity index decreased and the chronicity index increased, with no significant differences detected between the two treatment groups [20].

**COMPARING THE ALMS MAINTENANCE TRIAL WITH THE MAINTAIN NEPHRITIS TRIAL**

The ALMS maintenance and MAINTAIN nephritis trial reached distinct conclusions about the relative benefit of MMF over AZA, with ALMS finding superiority and MAINTAIN failing to find superiority of MMF. Table 1 compares the baseline characteristics of the two trials, while Table 2 compares the outcomes and adverse events between them. Some important differences between the design and conduction of these trials merit further discussion.

Perhaps the most notable difference between the two studies concerns the demographics of the study populations (Table 1). ALMS was an international study that enrolled a significant proportion of non-Caucasian patients (with one-third of all patients identified as Hispanic ethnicity), whereas MAINTAIN was a European study predominantly comprised of Caucasians (79%). The prognostic importance of race and ethnicity in lupus nephritis outcomes has been well demonstrated [21, 22], and thus the superiority of MMF detected in the ALMS trial may be at least partially explained by the higher risk population enrolled. Indeed, differential responses to therapy based on race/ethnicity were also suggested in the induction phase of the ALMS trial: while MMF was not superior to IVC for induction therapy in the overall cohort, in subgroup analyses, patients grouped as ‘other’ (mostly black and mixed-race patients) and Hispanic patients had significantly better response rates with MMF. It is worth noting, however, that despite the lower proportion of Caucasian patients in ALMS, there was in fact a greater absolute number of Caucasians in ALMS (99 patients) than MAINTAIN (83 patients) due to ALMS’ overall larger size. Furthermore, in ALMS, MMF’s superiority was not specific to non-Whites and in fact was consistent across all racial groups. Thus, the lower proportion of Caucasians in ALMS compared with MAINTAIN does not preclude the possibility of MMF’s superiority in this population.

Another important difference between the ALMS and MAINTAIN trials were the different induction regimens employed and the timing of randomization. The ALMS patients received either high-dose ‘NIH protocol’ IVC or MMF, whereas the MAINTAIN patients uniformly received low-dose ‘Euro-Lupus’ IVC. Furthermore, the maintenance phase of
Table 1. Baseline study characteristics

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<tr>
<td>Number of patients</td>
<td>227</td>
<td>105</td>
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<tr>
<td>Demographics</td>
<td>Race: 43.6% White, 10.1% Black, 33.5% Asian, 12.8% Other, Ethnicity: 33.9% Hispanic</td>
<td>Race: 79% White, 12.4% Black, 8.6% Asian, Ethnicity: 0% Hispanic</td>
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<tr>
<td>Baseline kidney function</td>
<td>SCr: 0.82–0.90 mg/dL (72.5–79.6 µmol/L) Proteinuria: 0.82–0.90 g/24 h</td>
<td>SCr: 1.01–1.02 mg/dL; (89.3–90.2 µmol/litre); Proteinuria: 2.94–3.63 g/24 h</td>
</tr>
<tr>
<td>Prior induction therapy</td>
<td>6 months of Rx with either MMF (up to 1 g tid) or 'NIH-protocol' IVC (0.5–1.0 g/m² BSA) qMonth</td>
<td>Low-dose IVC; (500 mg q2week × 6)</td>
</tr>
<tr>
<td>Maintenance steroid treatment</td>
<td>88% treated with prednisone (≤10 mg/day)</td>
<td>100% treated with prednisone taper</td>
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<td>Follow-up period</td>
<td>36 months</td>
<td>48 months</td>
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SCr, serum creatinine; MMF, mycophenolate mofetil; IVC, intravenous cyclophosphamide.

Table 2. Outcomes and adverse events

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<td>Primary endpoint</td>
<td>Time to treatment failure (composite endpoint); P = 0.003 in favor of MMF</td>
<td>Time to renal flare; no significant difference between MMF and AZA</td>
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<tr>
<td>Incidence of key endpoints (event rates in AZA/MMF groups)</td>
<td>Treatment failure: 32.4%/16.4%; renal flare: 23.4%/12.9%; Doubling of SCr: 4.5%/0.9%; ESRD: 2.7%/0%</td>
<td>Renal flare: 25%/19%; doubling of SCr: 7.7%/5.7%; ESRD: 1.9%/1.8%</td>
</tr>
<tr>
<td>Adverse events (event rates in AZA/MMF groups)</td>
<td>Leukopenia: 36.0%/22.6%; infection: 78.4%/79.1%; death: 0.9%/0%</td>
<td>Leukopenia: 21.2%/3.8%; Infection: 48%/60%; death 0%/3.8%</td>
</tr>
<tr>
<td>Withdrawal rate (AZA/MMF)</td>
<td>51.3%/37.1%</td>
<td>17.3%/28.3%</td>
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</table>

Scrub, serum creatinine; MMF, mycophenolate mofetil; AZA, azathioprine; ESRD, end-stage renal disease.

ALMS included only the 227 patients who responded to induction therapy, and were subsequently re-randomized to a maintenance strategy, whereas MAINTAIN included all patients regardless of response to induction (indeed they were randomized only once, at study entry). It may therefore be possible that MMF is superior to AZA only if starting from an attained remission.

There were subtle but important differences in the endpoints and outcomes of the trials (Table 2). MAINTAIN, the negative study, was a smaller trial, with 105 patients compared with 227 in ALMS maintenance. In MAINTAIN, renal flares occurred in 19% of the MMF group and 25% of the AZA group, a non-significant difference. However, while the trial was designed to detect what the authors considered a ‘clinically meaningful’ difference of 10% in renal flares, both the groups had a much lower proportion of flares than anticipated in the power calculation (35% predicted in the AZA group). This left the trial underpowered, as shown by the wide CI for the hazard ratio (0.33–1.71). It is conceivable that a larger trial, similar to ALMS, might have found a significant and clinically meaningful difference.

The ALMS trial was sponsored by Vifor Pharma (formerly Aspreva Pharmaceuticals), a Canadian pharmaceutical company that produces MMF under the brand name Cellcept, whereas the MAINTAIN trial was investigator-sponsored and did not receive industry funding. While the industry sponsorship undoubtedly demands a higher level of scrutiny of positive trials [23–25], ALMS employed a rigorous double-blind randomization strategy in which both groups received a placebo identical to the non-administered drug (a ‘double-dummy’ design). MAINTAIN, on the other hand, utilized a less-desirable open-label design. Overall, the raised skepticism warranted by ALMS’ industry sponsorship may be alleviated by the scrupulousness of the study design.

Perhaps the most peculiar difference between ALMS and MAINTAIN was the disparate rates of and reasons for patient withdrawal. The overall withdrawal rate in the ALMS maintenance trial was almost double that observed in MAINTAIN: 44% versus 23%, respectively. In ALMS, withdrawals were more common in the AZA group (51% of patients versus 37% in the MMF group) and were mostly due to adverse events, which were more common with AZA. While analysis of specific adverse events is limited by concerns for statistical power and multiple hypothesis testing, leucopenia and non-nephritic systemic lupus erythematosus flares appeared significantly more common in the AZA group, whereas gastroenteritis was significantly more common in the MMF group.
Pregnancy in ALMS was considered a serious adverse event and grounds for the cessation of the study drug. A numerically larger but statistically insignificant number of subjects in the AZA group became pregnant or had elective abortions compared with the MMF group (six pregnancies and three abortions in the AZA group, compared with three and two, respectively, in the MMF group), although it was not reported how many patients withdrew because of desired pregnancy. In MAINTAIN, on the other hand, withdrawals were much fewer and, in general, easier to explain. There were more withdrawals in the MMF group (28% versus 17% in the AZA group) and these were largely driven by pregnancy or desire for pregnancy. This is coherent with the better safety data for AZA in pregnancy compared with MMF, and so with the open-label design it is probable that subjects taking AZA would be less likely to quit the trial in order to pursue pregnancy.

**CONCLUSIONS**

Despite their differences, the ALMS maintenance and MAINTAIN nephritis trials demonstrate that maintenance therapy with either MMF or AZA is overall well tolerated and leads to excellent results at 3–4 years of follow-up in the majority of patients. Both agents yielded extremely low rates of doubling of SCr, ESRD and death. An important lesson is that an extended duration of maintenance therapy is well tolerated, at least over a 3–4 year period, and can therefore provide an extended period of protection from disease recurrence or relapse. The ALMS trial suggests that MMF may be more effective and better tolerated than AZA, especially in higher-risk minority patients. For a Caucasian patient, the agent of choice is less clear in light of the MAINTAIN findings. However, as discussed earlier, the superiority of MMF demonstrated in ALMS may have been missed in MAINTAIN due to under-powering and the inclusion of patients not in full remission. Therefore, while either drug was associated with good outcomes in Caucasians, we generally favor MMF even in this population. For pregnant patients and those planning pregnancy, AZA is clearly the drug of choice. Further studies would be needed to confirm these suggestions as to the choice of the agents. Realistically, we are unlikely to see such studies performed in light of the extensive work that has already been done on these medications, both of which are now off-patent and available in generic forms. For now, clinicians should feel confident when using either of these agents for the maintenance treatment of lupus nephritis.

**CONFLICT OF INTEREST STATEMENT**

Dr Appel received grant support from Aspreva Pharmaceuticals (now Vifor Pharma) as an investigator for the ALMS and ALMS-maintenance trials. He has served as a consultant for Aspreva-Vifor, Roche and Genentech. He has no stock holdings or other investments in these companies. The contents of this paper have not been published previously either in whole or part.

**REFERENCES**


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Contrast-induced acute kidney injury: how much contrast is safe?

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Keywords: acute kidney injury, contrast media, contrast ratio, glomerular filtration rate ratios, which can be used by clinicians to effectively lower the incidence of CI-AKI in their patients.

ABSTRACT

Iodinated contrast media (CM) are used in many investigations that a patient may undergo during the course of an inpatient stay. For the vast majority of patients, exposure to CM has no sequelae; however, in a small percentage, it can result in a worsening in renal function termed contrast-induced acute kidney injury (CI-AKI). CI-AKI is one of the leading causes of in-hospital renal dysfunction. It is associated with a significant increase in morbidity and mortality as well as an increased length of hospital stay and costs. Unfortunately, the results of extensive research into pharmacological inventions to prevent CI-AKI remain disappointing. In this article, we briefly outline the pathophysiological mechanisms by which iodinated CM may cause CI-AKI and discuss the evidence for reducing CI-AKI by limiting contrast volumes. In particular, we review the data surrounding the use of contrast volume to

INTRODUCTION

Almost 60 years ago, the first case of contrast-induced acute kidney injury (CI-AKI) was described in a patient with multiple myeloma receiving intravenous pyelography [1]. Currently, intravascular contrast agents are the third most common cause of AKI in hospitalized patients, accounting for 10–13% of cases [2, 3]. The growth in incidence in CI-AKI over the decades is not surprising. In 2003, ~80 million doses of iodinated contrast media (CM) were prescribed worldwide [4]. The recipients of this contrast have, on average, become older with increased risk factors for CI-AKI such as diabetes mellitus (DM) and baseline chronic kidney disease (CKD).