**Long title: Outcomes following mycophenolate mofetil versus cyclophosphamide induction treatment for proliferative Juvenile-onset Lupus Nephritis**

**Short title: MMF vs IVCYC in Juvenile-onset LN**

**Eve MD Smith1,2, Eslam Al-Abadi3, Kate Armon4, Kathryn Bailey5, Coziana Ciurtin6, Joyce Davidson7, Janet Gardner-Medwin8, Kirsty Haslam9, Dan Hawley10, Alice Leahy11, Valentina Leone12, Flora McErlane13, Devesh Mewar14, Gita Modgil15, Robert Moots16, Clarissa Pilkington17, Athimalaipet Ramanan18, Satyapal Rangaraj19, Phil Riley20, Arani Sridhar21, Nick Wilkinson22, Michael W Beresford 1,2, Christian M Hedrich1,2**

1Department of Women and Children’s Health, Institute of Translational Medicine, University of Liverpool, Liverpool, UK.

2Department of Paediatric Rheumatology, Alder Hey Children’s NHS Foundation Trust, Liverpool, UK.

3Department of Rheumatology, Birmingham Children’s Hospital, Birmingham, UK.

4Department of Paediatric Rheumatology, Cambridge University Hospitals, Cambridge, UK.

5Department of Paediatric Rheumatology, Oxford University Hospitals, Oxford, UK.

6Department of Rheumatology, University College London Hospitals NHS Foundation Trust, London, UK.

7Department of Paediatric Rheumatology, Royal Hospital for Sick Children, Edinburgh, UK.

8Department of Paediatric Rheumatology, NHS Greater Glasgow and Clyde (Yorkhill Division), Glasgow, UK.

9Department of Paediatrics, Bradford Royal Infirmary, Bradford, UK.

10Sheffield Children's Hospital, Sheffield, UK.

11Department of Paediatric Rheumatology, Southampton General Hospital, Southampton, UK.

12Department of Paediatric Rheumatology, Leeds General Infirmary, Leeds, UK.

13Department of Paediatric Rheumatology, Royal Victoria Infirmary, Newcastle upon Tyne, UK.

14Department of Rheumatology, Royal Liverpool University Hospital, Liverpool, UK.

15Department of Paediatrics, Musgrove Park Hospital, Taunton, UK.

16Department of Rheumatology, University Hospital Aintree, Liverpool, UK.

17Department of Paediatric Rheumatology, Great Ormond Street Hospital, London, UK.

18Department of Paediatric Rheumatology, Bristol Royal Hospital for Children,

Bristol, UK.

19Department of Paediatric Rheumatology, Nottingham University Hospitals

Nottingham, UK.

20Department of Paediatric Rheumatology, Royal Manchester Children’s Hospital, Manchester, UK.

21Department of Paediatrics, Leicester Royal Infirmary, Leicester, UK.

22Guy's & St Thomas's NHS Foundation Trust, Evelina Children's Hospital, London, UK.

**Corresponding author:** Eve MD Smith. Institute in the Park, University of Liverpool, Alder Hey Children's Hospital, Eaton Rd, Liverpool, L12 2AP, [esmith8@liverpool.ac.uk](mailto:esmith8@liverpool.ac.uk)

**Background:** Juvenile-onset Systemic Lupus Erythematosus (JSLE) is more severe than adult-onset disease, including more lupus nephritis (LN). Despite differences in phenotype/pathogenesis, treatment is based upon adult trials. This study aimed to compare 1) treatment response, 2) damage accrual, 3) time to inactive LN, and 4) subsequent flare, in JSLE LN patients treated with mycophenolate mofetil (MMF) vs. intravenous cyclophosphamide (IVCYC).

**Methods:** UK JSLE Cohort Study participants, ≤16-years at diagnosis, with ≥4 ACR criteria for SLE, with class III or IV LN, were eligible. Mann-Whitney U tests, Fisher’s exact and Chi-squared tests utilised.

**Results:** 34/51(67%) received MMF, and 17/51(33%) received IVCYC. No significant differences were identified at 4-8, 10-14 months post renal biopsy, and last follow-up, in terms of renal-BILAG scores, urine albumin/creatinine ratio, serum creatinine, ESR, anti-dsDNA-antibody, C3-levels and patient/physician global scores. Standardised Damage Index scores did not differ between groups at 13 months, or last follow-up. Inactive LN was attained 262[141-390] days after MMF treatment, and 151[117-305] days following CYC (*p=0.17*). Time to renal flare was 451[157-1266] days for MMF, and 343[198–635] days for CYC (*p=0.47*)).

**Conclusion:** This is the largest study to date investigating induction treatments for proliferative LN in children, demonstrating comparability of MMF and IVCYC.

**Keywords:** Lupus Erythematosus, Systemic. Lupus nephritis. Mycophenolic Acid. Cyclophosphamide.

**Word count: 2201**

**Introduction**

Juvenile-onset systemic lupus erythematosus (JSLE), also known as childhood-onset SLE, comprises approximately 15-20% of all systemic lupus erythematosus (SLE) cases. Significant differences exist between JSLE and adult-onset SLE (aSLE), with JSLE patients displaying a more aggressive disease course 1-3, including more renal involvement. Up to 80% of JSLE patients develop Lupus Nephritis (LN) 1, compared with only 40-50% of adult SLE patients 4, 5. JSLE patients have higher mean SLE disease activity index (SLEDAI) scores at diagnosis and over their disease course 2, 4, 5. Furthermore, JSLE patients exhibit greater corticosteroid and immunosuppressive treatment burden over time 2, 4, 5, with more rapid accrual of disease related damage as compared to aSLE cohorts 2, 5, 6.

Despite differences in the phenotype and pathogenesis of JSLE vs. aSLE 7, even international recommendations for the treatment of JSLE itself 8 and LN specifically 9 are largely based upon data arising from adult SLE clinical trials. Head-to-head comparisons of induction treatments for proliferative, class III/IV International Society of Nephrology/Renal Pathology Society (ISN/RPS) LN in children are lacking. The largest paediatric study available retrospectively compared renal outcomes from seven patients treated with intravenous cyclophosphamide (IVCYC) and six individuals treated with mycophenolate mofetil (MMF) 10. This demonstrated a non-statistically significant trend towards more MMF treated patients achieving LN remission at six months. A randomized, open-label, non-inferiority trial including 140 American adult SLE patients, suggested MMF to be more effective than IVCYC 11. Notably in this study, 56% of patients included were of Black race, and 17% were White. A further study including 370 adult SLE patients did not detect significant differences in renal response rates between IVCYC and MMF induction treatment 12. A recent meta-analysis of available randomized trials in adults with LN (including 4,222 participants across 53 studies), demonstrated MMF, calcineurin inhibitors, or their combination to be most effective for inducing LN remission, as compared to IVCYC 13.

The aim of this present study was to use prospectively collected data from the UK JSLE Cohort Study1, to compare effectiveness of MMF vs. IVCYC induction treatments in patients with juvenile-onset LN, assessing response to treatment, damage accrual, time to achievement of inactive LN, and time to subsequent LN flare.

**Materials and methods**

*Patients*

Participants of the UK JSLE Cohort Study 1, monitored between 2006-2018, aged ≤16 years at the time of diagnosis and with ≥4 American College of Rheumatology (ACR) SLE classification criteria were included in this study if they had a renal biopsy result demonstrating ISN/RPS class III or IV LN 14. Patients were excluded if there was inadequate follow-up data to assess response to treatment over the first year. Patients with class III and IV LN were grouped according to whether they received MMF or IVCYC as induction treatment. Concomitant corticosteroid treatment was also documented (oral prednisolone, IV methylprednisolone (IVMP) or both). Self-reported ethnicity information was collected in accordance with the UK National Census categorisations 15. Data of patients who were of mixed race were grouped with those of the associated ethnic minority group. Written patient assent/consent and parental consent was obtained to participate in the UK JSLE Cohort Study, and full ethical approval was in place from the National Research Ethics Service North West, Liverpool East, UK (reference 06/Q1502/77). The research was carried out in accordance with the declaration of Helsinki.

*Clinical data for assessing response to treatment*

At a) baseline, b) 4-8, and c) 10-14 months post-biopsy, and d) the patients last visit, renal parameters (urine albumin:creatinine ratio, serum creatinine and the renal domain of the BILAG score), global disease activity parameters (erythrocyte sedimentation rate (ESR), anti-double stranded DNA antibodies (ds-DNA) and complement factor 3 (C3)) and patient/physician global scores (both 0-100 scale) were collected.

*Assessment of LN disease activity and damage*

The British Isles Lupus Assessment Grade (BILAG) score is a composite disease activity measure focusing on nine organs/systems (constitutional, mucocutaneous, neurological, musculoskeletal, cardiovascular/respiratory, renal, gastrointestinal, opthalmic and haematological). The BILAG score focuses on capturing disease transitions, with the clinician being asked to grade clinical features as new, the same, worse or improving over the last 4 weeks and as compared to the preceding 4 weeks, facilitating accurate assessment of new activity, flare, remission in individual organs/systems 16.

The renal domain of the paediatric British Isles Lupus Assessment Grade 2004 (pBILAG2004) disease activity score 1 was used to assess LN disease activity longitudinally. This was calculated from proteinuria, blood pressure, serum creatinine, glomerular filtration rate (GFR), active urine sediment, and recent renal biopsy findings. The renal pBILAG score is graded A-E and defined as follows; pBILAG2004 grade A/B: severe, moderate disease respectively, grade C patients: mild/improving renal disease, grade D: inactive disease but previous system involvement, grade E: system has never been involved 16. The renal pBILAG score was used to define a change in LN activity; with attainment of inactive LN seen when the renal BILAG score changed from A, B or C to D; or subsequent flare following initial response to treatment when the renal pBILAG score changed from D to A or B. JSLE related damage was assessed using the Systemic Lupus International Collaborating Clinics Standardised Damage Index (SLICC-SDI) score 17 at 10-18 months post renal biopsy.

*Statistical analysis*

Renal parameters, global disease activity parameters and patient/physician global scores were compared between patients who received MMF or IV CYC as induction treatment. Results are displayed as median values with interquartile ranges or counts and percentages. The data was non-normally distributed (Shapiro-Wilk test), therefore non-parametric tests were employed. Mann-Whitney U tests for continuous data and Fisher’s exact or Chi-squared tests for categorical data. All analysis was undertaken in PRISM version 6.0.

**Results**

At the time of data analysis (April 2018), the study cohort consisted of 411 UK JSLE Cohort Study patients meeting general inclusion criteria, with 69/411 (17%) having proliferative LN (ISN/RPS class III or IV LN). Of these, 18/69 (29%) were excluded due to insufficient follow-up leaving 51 who were subsequently considered. 34/51 (67%) received MMF (13/34 (38%) class III, 21/34 (62%) class IV LN), and 17/51 (33%) received IVCYC (8/17 (47%) class III, 9/17 (53%) class IV LN) as induction therapy (see Figure 1). Of those who received MMF induction treatment, 17/34 (50%) received concomitant oral prednisolone and the other 17/34 (50%) received both IVMP and oral prednisolone. Within the IVCYC induction treatment group, 2/17 (12%) received oral prednisolone only and 15/17 (88%) received both IVMP and oral prednisolone.

*Patient demographics*

There were no statistically significant differences between the groups receiving induction therapy with MMF and IVCYC in terms of demographic factors at baseline, including gender, ethnicity, age at diagnosis and age at LN onset (all *p>0.05*, see Table 1).

*Response to treatment and damage accrual*

No statistically significant differences were identified between the MMF and IVCYC induction treatment groups at 4-8, 10-14 months post renal biopsy, and last follow-up, in terms of renal-pBILAG score, urine albumin/creatinine ratio, serum creatinine, ESR, anti-dsDNA antibody, C3 levels and patient/physician global scores (all *p>0.05,* see Table 2).The last follow-up visit occurred after a median of 4.2 years [2.2-7.2] for the MMF treatment group and 3.3 years for the IVCYC group [2.1-5.3]. JSLE-related damage did not differ between treatment groups after a median of 13 months [range 10-18 months] post renal biopsy, with medianSLICC-SDI scores of 0 [0-1.0] in the MMF group, and 0 [0-2.5] in the IVCYC group (*p = 0.67*). Similarly, at the time of the last follow-up, no difference in SLICC-SDI score could be identified (MMF group = 1.0 [0-1.0], IVCYC group = 0 [0-2.5], *p = 0.90*, see Table 3).

*Time to achievement of inactive LN and subsequent flare*

A state of renal pBILAG-defined inactive LN (score = D) was reached in 29/34 (85%) patients who received MMF induction treatment and 14/17 (82%) patients who received IVCYC (*p = 1.00*). Inactive LN took a median of 262 days [141–390] to achieve after MMF treatment, and 151 days [117-305] following IVCYC treatment (*p = 0.17*). Similar proportions of patients had a subsequent LN flare (renal BILAG of D changed to A or B) regardless of the treatment group; 20/29 (69%) MMF treated and 7/14 (50%) IVCYC treated (*p = 0.32*). The time to subsequent flare was also comparable between the two patient groups; median of 451 days [157-1266] for MMF treated, and 343 days [198-635] for IVCYC treated patients (*p = 0.47*).

**Discussion**

The aim of this study was to compare the effectiveness of MMF vs. IVCYC as induction treatments in children with LN, using data from the UK JSLE Cohort Study. Within the predominantly Caucasian JSLE study population, MMF and IVCYC were comparably efficacious with regards to treatment response and damage accrual as quantified in this study, and time to next LN flare. Remission was reached slightly sooner with IVCYC. However, differences did not reach statistical significance. Of note, within this real world UK study, more patients received MMF than CYC as induction therapy for class III/IV LN (34/51 (67%) received MMF and 17/51 (33%) received IVCYC). The choice of LN induction treatment (MMF or IVCYC) was based upon individual physician’s choice, with no specific guidelines on LN treatment in the UK. Results from the presented study highlight the need for prospective comparison of MMF vs. IVCYC induction treatment to better inform LN treatment protocols for children, especially given IVCYC’s poor safety profile 11, 12. Monitoring of MMF levels, with concentration-controlled dose adjustments has been shown to be associated with optimized mycophenolic acid exposure and an excellent renal outcome at 12 months of follow-up in a small sample of adult SLE patients with LN 18, therefore monitoring of MMF levels could be considered within such a prospective study.

Observations here are complementary to those of Lau *et al.* 10 who studied a much smaller cohort of American JSLE patients with class III LN (n=13), and demonstrated a comparable response following MMF or IVCYC induction treatment. The authors reported that at 6 months, no patient had achieved complete remission in the IVCYC group, while 57% were in partial remission. In the MMF group, 66% had achieved complete remission, 17% were in partial remission, and 17% were not in remission, leading to the conclusion that MMF may be superior to IVCYC for inducing remission at 6 months, although the small patient numbers precluded any meaningful statistical analysis. The current study differs from reports of Lau *et al.* in that both class III and IV LN patients were included, and patient numbers allowed for meaningful statistical analyses. Class III and IV LN patients were grouped in the current study on the basis that the recommended treatment for both classes of LN is the same 19-21. Further sub-dividing them was precluded by the sample size, especially within the CYC treatment group. These data also support the Single Hub and Access point for paediatric Rheumatology in Europe (SHARE) LN recommendations to use MMF as an induction agent for LN 9.

Results of the current presented study are also in-keeping with the reports from Appel *et al*. in aSLE 12, which is the largest study to date comparing MMF vs. IVCYC induction treatment, albeit in adult patients. It comprises a similar group of patients to the current study regarding race (US American; 39% White, 33% Asian, 27% ‘other race’ vs. 47% White, 35% Asian and 18% ‘other’ in the current UK JSLE Cohort Study). Appel *et al.* did not detect significant differences in renal response rates between IVCYC and MMF induction treatment 12. Furthermore, no differences were seen between the MMF and IVCYC groups in relation to adverse events, or infections. We are unable to comment on this within the current study, since these data are not collected within the UK JSLE Cohort Study.

Despite being the largest JSLE study to date comparing response to MMF vs. IVCYC for LN induction treatment, patient numbers included are relatively small. As per the inclusion criteria for this study, we only considered patients with class III or IV LN rather than all LN patients, for which these treatments are indicated, limiting the number LN patients available for inclusion. The UK JSLE Cohort Study collects patient data alongside routine clinical care. Therefore, reported clinical parameters, patient/physican global scores, SDI damage data and treatment regimens are recorded over a range of follow-up times post biopsy, rather than at exact time points. The length of follow-up also varied somewhat between patient groups in the current study, with MMF treated patients being followed for a median of 4.2 years [IQR 2.2-7.2] and IVCYC patients for 3.3 years [2.1-5.3] (although this did not reach statistical significance). Corticosteroid treatment regimens, MMF and CYC dosages may not be identical between centres and treating clinicians, as would be expected within a randomised control trial. However, class III and IV LN patients are usually treated with high-dose IVMP pulses (10-30 mg/kg/day, max. 1000mg on three consecutive days every 4 weeks) and oral corticosteroids (0.5-2 mg/kg/day, followed by a taper). MMF treatment in the UK usually follows the EUROLUPUS protocol22; and CYC is usually administered at 500-1000mg/m2/day every 4 weeks for a total of 4-6 months. The UK JSLE Cohort Study does not collect sufficient data to compare safety profiles of CYC vs. MMF treatments. Rigorous safety data is particular difficult to collect retrospectively. In light of these limitations, prospective comparison of MMF vs. IVCYC induction treatment in larger, ethnically diverse JSLE cohorts, whilst monitoring treatment adherence (e.g. MMF levels), controlling MMF, CYC and corticosteroid dosage (IV and oral), whilst recording drug safety is warranted to better inform treatment decisions for patients with LN.

**Conclusions**

This is the largest study to date investigating induction treatments for proliferative LN in JSLE. In predominantly Caucasian JSLE populations, MMF and IVCYC appear to be comparably efficacious in regard to treatment response, damage accrual, and time to next flare. Future prospective comparison of MMF vs. IVCYC treatment is warranted in ethnically diverse international JSLE cohorts to inform LN treatment protocols, and to explore the relative safety of both treatment regimens.

**Acknowledgements**

The authors would like to acknowledge all patients and their families for participating in this Study. Specifically, the authors are grateful to all the support given by the entire multi-disciplinary team within each of the paediatric centres who are part of the UK JSLE Study Group (https://www.liverpool.ac.uk/translational-medicine/research/ukjsle/jsle/). The study was supported by the National Institute of Health Research (NIHR) Clinical Research Network (CRN): Children’s National Specialty Group and CRN Research Nurses and staff in both UK centres, the NIHR Alder Hey Clinical Research Facility for Experimental Medicine, and all those who have supported the work of the UK JSLE Study Group to date. Special recognition also goes to Dr Duncan Appleby for database and information technology support and Carla Roberts for co-ordination of the UK JSLE Cohort study.

**Conflict of interest:** The Authors declare that there is no conflict of interest.

**Funding support:** This work was supported by Lupus UK, who provide financial support for co-ordination of the UK JSLE Cohort Study [grant numbers: LUPUS UK: JXR10500, JXR12309]. The study took place as part of the UK’s ‘Experimental Arthritis Treatment Centre for Children’ supported by Arthritis Research UK (grant number ARUK-20621), the University of Liverpool, Alder Hey Children’s NHS Foundation Trust and the Alder Hey Charity, and based at the University of Liverpool and Alder Hey Children’s NHS Foundation Trust. The funding bodies detailed above were not involved in the design, collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication.

**Authors’ contributions:**

EMDS, MWB and CMH led on the conception and design of the study. ES performed the statistical analysis. All authors participated in the acquisition of and interpretation of the data. MWB is Chief Investigator of the UK JSLE Cohort Study. All authors were involved in drafting the manuscript and revising it critically for important intellectual content. They have also all read and given final approval of the version to be published.

**Availability of data and material**

Access to the data associated with this study can be requested by interested investigators by contacting the chief investigator of the UK JSLE Cohort Study Prof Michael Beresford (m.w.beresford@liverpool.ac.uk), on reasonable request.

**References**

1. Watson L, Leone V, Pilkington C, et al. Disease activity, severity, and damage in the UK Juvenile-Onset Systemic Lupus Erythematosus Cohort. *Arthritis Rheum* 2012; 64: 2356-2365.

2. Tucker LB, Uribe AG, Fernandez M, et al. Adolescent onset of lupus results in more aggressive disease and worse outcomes: results of a nested matched case-control study within LUMINA, a multiethnic US cohort (LUMINA LVII). *Lupus* 2008; 17: 314-322.

3. Mina R and Brunner HI. Pediatric lupus-are there differences in presentation, genetics, response to therapy, and damage accrual compared with adult lupus? *Rheum Dis Clin North Am* 2010; 36: 53-80.

4. Tucker LB, Menon S, Schaller JG, et al. Adult- and childhood-onset systemic lupus erythematosus: a comparison of onset, clinical features, serology, and outcome. *British Journal Rheumatology* 1995; 34: 866-872.

5. Brunner HI, Gladman DD, Iban ̃ez D, et al. Difference in Disease Features Between Childhood-Onset and Adult-Onset Systemic Lupus Erythematosus. *Arth & Rheum* 2008; 58: 556-562.

6. Gutierrez-Suarez R, Ruperto N, Gastaldi R, et al. A proposal for a pediatric version of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index based on the analysis of 1,015 patients with juvenile-onset systemic lupus erythematosus. *Arthritis Rheum* 2006; 54: 2989-2996. DOI: 10.1002/art.22048.

7. Hedrich CM, Smith EMD and Beresford MW. Juvenile-onset systemic lupus erythematosus (jSLE) - Pathophysiological concepts and treatment options. *Best Pract Res Clin Rheumatol* 2017; 31: 488-504. DOI: 10.1016/j.berh.2018.02.001.

8. Groot N, de Graeff N, Avcin T, et al. European evidence-based recommendations for diagnosis and treatment of childhood-onset systemic lupus erythematosus: the SHARE initiative. *Ann Rheum Dis* 2017; 76: 1788-1796. DOI: 10.1136/annrheumdis-2016-210960.

9. Groot N, de Graeff N, Marks SD, et al. European evidence-based recommendations for the diagnosis and treatment of childhood-onset lupus nephritis: the SHARE initiative. *Ann Rheum Dis* 2017; 76: 1965-1973. DOI: 10.1136/annrheumdis-2017-211898.

10. Lau KK, Ault BH, Jones DP, et al. Induction therapy for pediatric focal proliferative lupus nephritis: cyclophosphamide versus mycophenolate mofetil. *J Pediatr Health Care* 2008; 22: 282-288. DOI: 10.1016/j.pedhc.2007.07.006.

11. Ginzler EM, Dooley MA, Aranow C, et al. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. *N Engl J Med* 2005; 353: 2219-2228. DOI: 10.1056/NEJMoa043731.

12. Appel GB, Contreras G, Dooley MA, et al. Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. *J Am Soc Nephrol* 2009; 20: 1103-1112. DOI: 10.1681/ASN.2008101028.

13. Palmer SC, Tunnicliffe DJ, Singh-Grewal D, et al. Induction and Maintenance Immunosuppression Treatment of Proliferative Lupus Nephritis: A Network Meta-analysis of Randomized Trials. *Am J Kidney Dis* 2017; 70: 324-336. DOI: 10.1053/j.ajkd.2016.12.008.

14. Weening JJ, D'Agati VD, Schwartz MM, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. *J Am Soc Nephrol* 2004; 15: 241-250.

15. Office for National Statistics. England and Wales National Census, <https://www.ons.gov.uk/census> (2017, accessed 11/5/18 2018).

16. Isenberg DA, Rahman A, Allen E, et al. BILAG 2004. Development and initial validation of an updated version of the British Isles Lupus Assessment Group's disease activity index for patients with systemic lupus erythematosus. *Rheumatology (Oxford)* 2005; 44: 902-906. DOI: 10.1093/rheumatology/keh624.

17. Gladman D, Ginzler E, Goldsmith C, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. *Arthritis Rheum* 1996; 39: 363-369.

18. Daleboudt GM, Reinders ME, den Hartigh J, et al. Concentration-controlled treatment of lupus nephritis with mycophenolate mofetil. *Lupus* 2013; 22: 171-179. DOI: 10.1177/0961203312469261.

19. Bertsias GK, Tektonidou M, Amoura Z, et al. Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. *Ann Rheum Dis* 2012; 71: 1771-1782. DOI: 10.1136/annrheumdis-2012-201940.

20. KIDOGO-consortium. Chapter 12: Lupus nephritis. *Kidney Int Suppl (2011)* 2012; 2: 221-232. DOI: 10.1038/kisup.2012.25.

21. Mina R, von Scheven E, Ardoin SP, et al. Consensus treatment plans for induction therapy of newly diagnosed proliferative lupus nephritis in juvenile systemic lupus erythematosus. *Arthritis Care Res (Hoboken)* 2012; 64: 375-383. DOI: 10.1002/acr.21558.

22. Houssiau FA, Vasconcelos C, D'Cruz D, et al. Immunosuppressive therapy in lupus nephritis: the Euro-Lupus Nephritis Trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. *Arthritis Rheum* 2002; 46: 2121-2131. DOI: 10.1002/art.10461.

**Table 1: Demographic details of the MMF and IV CYC treated groups at baseline**

|  |  |  |  |
| --- | --- | --- | --- |
| **Demographics** | **MMF induction**  **(n=34)** | **IV CYC induction**  **(n=17)** | ***p-value*** |
| **Gender** | F = 27 (79%)  M = 7 (21%) | F = 14 (82%)  M = 3 (18%) | *1.0* |
| **Race**   * White British * Asiana * African / Caribbeanb * Other Caucasian origin | 16 (47%)  11 (32%)  6 (18%)  1 (3%) | 8 (47%)  7 (41%)  1 (6%)  1 (6%) | *0.81* |
| **Age at diagnosis (years)** | 12.6 [9.0-14.8] | 13.3 [12.1-15.1] | *0.10* |
| **Age at biopsy (years)** | 13.3 [11.2-15.0] | 13.6 [12.8-15.6] | *0.20* |

aAsian origin included Bangladeshi, Indian and Pakistani patients. bAfrican/Caribbean included patients of African, Caribbean, mixed White and Black African and mixed White and Caribbean origin. Counts and percentages or median values with interquartile ranges displayed. Mann-Whitney U tests used for continuous data Chi-squared tests for categorical data. MMF, Mycophenolate Mofetil. IV, intra-venous. CYC, Cyclophosphamide. F, female. M, male. ACR, American College of Rheumatology.

**Table 2: Comparison of JSLE clinical parameters and patient/physican global scores following MMF vs. IV CYC treatment.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Time post biopsy** | **Outcome parameter** | **MMF treated** | **IV CYC treated** | ***p-value*** |
| **4-8 months** | **Renal pBILAG scorea** | A – 3 (12%)  B – 9 (35%)  C – 3 (12%)  D – 11 (41%) | A – 2 (14%)  B – 2 (14%)  C – 4 (28%)  D – 6 (44%) | *1.0* |
| **Urine albumin / creatinine ratio (mg/mmolCr)** | 27 [12.8 – 96.4] | 9 [1.3 – 67] | *0.46* |
| **Serum creatinine (μmol/l)** | 60.0 [47.5 – 75.0] | 59.5 [49.8 – 75.0] | *0.86* |
| **Patient global (0-100)** | 10 [0 – 47.0] | 16 [0 – 32.2] | *0.71* |
| **Physician global (0-100)** | 11 [1.5 - 25.5] | 7.8 [5.0 – 31.5] | *0.71* |
| **ESR (mm/h)** | 10.5 [3.3-20.8] | 23.5 [10.8 – 77.8] | *0.07* |
| **dsDNA (IU/l)** | 54.0 [29.6 – 88.9] | 81.5 [0 – 270.0] | *0.84* |
| **C3 (g/L)** | 1.04 [0.87 -1.32] | 0.88 [0.78 – 0.99] | *0.08* |
| **10-14 months** | **Renal pBILAG scoreb** | A – 1 (4%)  B – 5 (19%)  C – 3 (11%)  D – 18 (66%) | A – 1 (7%)  B – 3 (21%)  C – 2 (14%)  D – 8 (58%) | *1.00* |
| **Urine albumin / creatinine ratio (mg/mmolCr)** | 13.25 [4.3 – 41.7] | 20.5 [ 3.0 – 56.4] | *0.99* |
| **Serum creatinine (μmol/l)** | 59 [51.0 – 69.0] | 62.0 [50.0 – 73.0] | *0.33* |
| **Patient global (0-100)** | 4.5 [0 – 9.3] | 3.0 [0.5 – 52.0] | *0.98* |
| **Physician global (0-100)** | 7.0 [1.3 – 14.0] | 9.9 [3.0 – 24.0] | *0.66* |
| **ESR (mm/h)** | 11.5 [5.0 – 20.8] | 20.0 [4.0 – 48.5] | *0.62* |
| **dsDNA (IU/l)** | 44.0 [24.0 – 94.8] | 20.4 [6.4 – 439.5] | *0.84* |
| **C3 (g/L)** | 0.98 [0.81 – 1.18] | 1.04 [0.92 – 1.34] | *0.21* |
| **Last visit** | **Renal pBILAG scorec** | A – 1 (3%)  B – 5 (16%)  C – 3 (9%)  D – 23 (72%) | A – 1 (7%)  B – 1 (7%)  C – 2 (14%)  D – 11 (72%) | *1.0* |
| **Urine albumin / creatinine ratio (mg/mmolCr)** | 21.0 [6.0 – 42.0] | 17.4 [8.0 – 116.9] | *0.81* |
| **Serum creatinine (μmol/l)** | 54.0 [46.0 – 59.0] | 62.0 [50.5 – 74.8] | *0.08* |
| **Patient global (0-100)** | 8.0 [0.0 – 30.0] | 2.0 [0.0 – 52.0] | *0.75* |
| **Physician global (0-100)** | 4.0 [0.0 – 15.0] | 4.0 [0.0 – 23.5] | *0.56* |
| **ESR (mm/h)** | 6.0 [3.0 -20.0] | 15.0 [5.5 – 52.0] | *0.09* |
| **dsDNA (IU/l)** | 51.3 [15.5 – 150.5] | 14.5 [5.4 – 129.8] | *0.28* |
| **C3 (g/L)** | 1.06 [0.92 – 1.24] | 1.14 [0.83 – 1.21] | *0.94* |

**a**Sufficient clinical data available to calculate the renal-pBILAG score in 26/34 MMF, and 14/17 CYC treated patients. Fishers exact test utilised to compare the proportion of active LN (renal-pBILAG domain A, B or C) to inactive LN patients (renal-pBILAG domain of D). bSufficient data to calculate the renal-pBILAG score in 27/34 MMF treated and 14/17 CYC treated patients. cSufficient clinical data to calculate the renal-pBILAG score in 32/34 MMF treated and 15/17 CYC treated patients. Median values/inter-quartile ranges quoted for clinical parameters and patient/physican global scores. Counts/percentages given for renal-pBILAG scores. Mann-Whitney U test used to compare the treatment groups. MMF, Mycophenolate Mofetil. IV, intra-venous. CYC, Cyclophosphamide. pBILAG, paediatric British Isles Lupus Assessment Grade. F, female. M, male. ACR, American College of Rheumatology. ESR, erythrocyte sedimentation rate. DsDNA, anti-double stranded DNA antibodies. C3, complement factor 3.

**Table 3: SLICC SDI damage scores at 10-18 months post renal biopsy and last follow-up visit.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Time** | **SLICC SDI** | | ***p-value*** |
| **MMF** | **IV CYC** |
| **10-18 months post biopsya** | 0 [0 - 1] | 0 [0 – 2.5] | *0.67* |
| **Last follow-upb** | 1.0 [0 – 1] | 0 [0 – 2.5] | *0.90* |

aSLICC SDI data available for 40/51 patients at 10-18 months post biopsy. bSLICC SDI data available for all 51 patients at last follow-up. Median values and inter-quartile ranges quoted, with Mann Whitney U test used to compare the treatment groups. SLICC-SDI, Systemic Lupus International Collaborating Clinics Standardised Damage Index score. MMF, Mycophenolate Mofetil. IV, intra-venous. CYC, Cyclophosphamide.