

## **Renal transplantation for lupus nephritis: non-adherence and graft survival.**

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## **Abstract**

### **Objectives**

Poor adherence to immunosuppressive treatment is common in patients with systemic lupus erythematosus and may identify those with lupus nephritis (LN) who have a poorer prognosis. Non-adherence has also been reported to be a potential adverse outcome predictor in renal transplantation (rTp). We investigated whether non-adherence is associated with increased rTp graft rejection and/or failure in patients with LN.

### **Methods**

Patients with LN undergoing rTp in two major London hospitals were retrospectively included. Medical and electronic records were reviewed for documented concerns of non-adherence as well as laboratory biochemical drug levels. The role of non-adherence and other potential predictors of graft rejection/ failure including demographics, comorbidities, age at SLE and LN diagnosis, type of LN, time on dialysis prior to rTp and medication use were investigated using logistic regression.

### **Results**

Out of 361 patients with LN, 40 had renal transplantation. During a median follow up of 8.7 years, 17/40 (42.5%) of these patients had evidence of non-adherence. A total of 12 (30.0%) patients experienced graft rejection or failure or both. In the adherent group 2/23 (8.7%) had graft rejection, whilst in the non-adherent this rose to 5/17 (29.4%,  $p=0.11$ ). Graft failure was seen in 5/23 (21.7%) patients from the adherent group and 4/17 (23.5%) in the non-adherent group ( $p=0.89$ ). Non-adherent patients had a trend towards increased graft

rejection, hazard ratio 4.38, 95% CI=0.73-26.12, p=0.11. Patients who spent more time on dialysis prior to rTp were more likely to be adherent to medication, p=0.01.

## **Conclusion**

Poor adherence to immunosuppressive therapy is common and has been shown to associate with a trend towards increased graft failure in patients with LN requiring renal transplantation. This is the first paper to report that shorter periods on dialysis prior to transplantation might lead to increased non-adherence in lupus patients.

## **Keywords**

- Lupus nephritis
- Adherence to treatment
- Renal transplant
- Graft rejection
- Graft failure
- SLE

## **Key messages**

- Non-adherence to immunosuppressive medication following renal transplantation in patients with lupus nephritis is common
- Non-adherence might lead to increased graft rejection following renal transplantation for lupus nephritis
- Longer periods on dialysis prior to renal transplantation are associated with improved adherence post-transplantation

## Introduction

According to the World Health Organization medication adherence is “the extent to which a person’s behaviour (taking medications, following a recommended diet and/or executing life-style changes) corresponds with the agreed recommendations of a health care provider <sup>1</sup>.” We and others have shown that adherence to medication is variable in patients with systemic lupus erythematosus (SLE), with poor adherence often affecting more than 50% of the patients; this might potentially be associated with worse overall prognosis <sup>2-4</sup>.

Renal transplantation for patients with lupus nephritis is an increasingly utilised therapy for end stage renal failure (ESRF) <sup>5,6</sup>. However, the sparsity of suitable donors and frequent allosensitisation of lupus patients due to receipt of blood products and prior pregnancies means that most patients spend significant time on dialysis before transplantation. Poor adherence to immunosuppressive therapy has been shown to associate with increased graft failure in renal transplant patients. Up to 16% of graft losses are attributed, in part, to poor adherence <sup>7,8</sup>.

It is recognised that in patients with renal transplantation non-adherence can lead to acute and chronic rejection, reduced renal function potentially necessitating return to dialysis and even death <sup>9</sup>. Returning to dialysis after a failed renal transplant is associated with a 78% mortality risk compared to patients on the transplant waiting list receiving dialysis <sup>10</sup>. However, despite the available evidence linking non-adherence to adverse outcomes in patients with transplantation, little specific is known regarding adherence in patients with

lupus nephritis following renal transplantation and whether less adherent patients have worse outcomes.

In this study we investigated potential factors leading to non-adherence in patients with SLE who underwent renal transplantation for LN and whether evidence of non-adherence associates with increased renal graft rejection, defined as an acute deterioration in the graft function associated with specific histopathological changes in the graft; or failure, defined as the need for dialysis or re-transplantation.

## **Methods**

All patients with diagnoses of both SLE and renal failure leading to renal transplantation from two major London hospitals (University College London, UCLH, and Royal Free Hospital, RFH) since 1975 were retrospectively identified and included in this study analysing prospectively captured data. All patients fulfilled  $\geq 4$  of the 1982 revised classification criteria for SLE of the American College of Rheumatology <sup>11</sup> and we used the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification system to define the histological class of lupus nephritis <sup>12</sup>. Patients receiving a transplant prior to 1982 were retrospectively shown to fulfil the 1982 criteria.

We retrospectively reviewed hospital electronic and paper records, correspondence with family practitioners and with other hospital physicians to identify any documented concerns about non-adherence to prescribed immunosuppressive treatment. Such concerns would usually be documented if the patients volunteered that they were not adherent to the medication themselves, by family members or admitting to this following direct questioning.

Furthermore, in the United Kingdom repeat prescriptions are facilitated by the General Practitioner looking after the patients in the community. Therefore, if the patients do not renew their prescriptions in the community, the General Practitioner or the pharmacist will quickly become aware of this and will bring this to the attention of the clinical team for further evaluation. A recent article revealed that although patient reporting could detect even relatively infrequently missed tablets, drug monitoring could also identify severe non-adherence<sup>3</sup>. Thus, we also reviewed the trough blood levels recorded for patients on tacrolimus or ciclosporin and mycophenolate mofetil (MMF) to help ascertain evidence of non-adherence. As there is no standard biochemical definition of non-adherence for patients with a renal transplant, we took a realistic and pragmatic approach of defining non-adherence as evidence of sub-therapeutic drug levels in routine measuring in >50% of the readings taken, at least 6 months after the renal transplantation to avoid levels taken during the initial introduction of the medication and individual dose adjusting. We used the percentage of sub-therapeutic trough levels of immunosuppressant medication as a surrogate marker of poor adherence rather than trough level variability, as the former has been reported to be more strongly associated with graft rejection after kidney transplantation<sup>7</sup>. Finally, we examined potential associations with poor adherence including sex, ethnicity, age at SLE diagnosis, age at lupus nephritis diagnosis, age when dialysis was started, duration of SLE diagnosis to LN histological type of LN, time on dialysis prior to transplantation, other existing conditions such as diabetes mellitus, hypertension, dyslipidaemia and prior cardiovascular disease. The primary end point was renal graft rejection (defined as acute deterioration in graft function with rejection confirmed histopathologically) occurring >12 months from the transplantation. Secondary endpoints included renal graft failure (defined as need for dialysis or re-transplantation) and a

composite endpoint of graft rejection and/or failure >12 months from the transplant. As such, if graft failure was identified the patients were censored for the purposes of the secondary outcomes, but continued to be monitored for the primary endpoint of renal graft rejection in the second transplant. The study was a retrospective review of a long-term observational registry and in effect an audit for which University College London does not require formal ethical permission.

### *Statistical analysis*

Categorical variables are presented as number and percentage whilst continuous variables are presented as mean and standard deviation (if normally distributed) or otherwise median and interquartile range. Comparisons between groups were performed using Student's *t*-test for normally distributed data or the Mann-Whitney U test for other data or Fisher's exact test. Logistic regression was used to investigate the potential association between non-adherence and renal graft rejection or failure. A  $p < 0.05$  was considered significant. IBM SPSS version 25 (IBM Corp., Armonk, NY, USA) was used for statistical analyses.

## **Results**

Three hundred and sixty-one patients with SLE were identified with lupus nephritis the vast majority biopsy confirmed (>90%), of who 40 had renal transplantation for lupus nephritis. A total of 17/40 (42.5%) patients were identified to be non-adherent to prescribed treatment for lupus nephritis (figure 1).

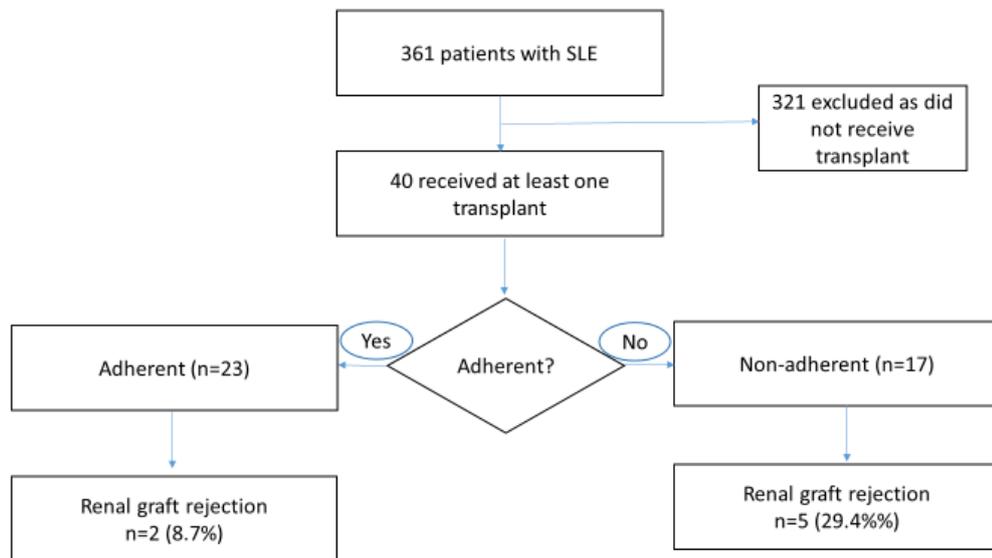


Figure 1: Flow diagram indicating the study population included in this cohort.

As shown in table 1, the only significant difference between the adherent and non-adherent groups was the amount of time spent on dialysis with the adherent group spending 33 (27-79) months on dialysis vs. the non-adherent group spending 17 (10-24) months on dialysis,  $p=0.01$ . There were no other significant differences in adherent and non-adherent patients. In particular, in this cohort there was no difference between the groups with regards to the age at SLE diagnosis or renal transplantation, gender, ethnicity, diagnosis duration, medication prescribed or donor source). In addition, there were no significant differences in other comorbidities between the two groups as shown in table 1 (all values  $p>0.05$ ). Furthermore, there was no difference in adherence vs non-adherence patterns in patients who had received rTp prior to the year 2000 or after this time. Moreover, there was no difference in the group that had ever received azathioprine or ciclosporin, to a group that had never received either of these medications in terms of adherence (all values  $p>0.05$ ).

This would support that even if immunotherapeutic regimes were modified during the period of the study, this was unlikely to affect the pattern of adherence/non-adherence.

One patient received three rTp in total and had rejection on the initial transplant. Two more patients received two rTp each. One had rejection on the initial graft whilst the second one did not have evidence of rejection either on the first or second graft.

Recording a concern about non-adherence either following medical consultation or biochemically, supported a trend to increased graft rejection. During a median follow up of 8.7 years, 17/40 (42.5%) of patients had evidence of non-adherence (table 1). A total of 12 (30.0%) patients experienced graft rejection or failure or both. From the adherent group 2/23 (8.7%) had graft rejection whilst from the non-adherent group this was 5/17 (29.4%,  $p=0.11$ ). Graft failure was seen in 5/23 (21.7%) patients from the adherent group and 4/17 (23.5%) in the non-adherent group ( $p=0.89$ ). Using Logistic regression, non-adherent patients had a trend towards increased renal graft rejection (HR 4.38, 95% CI 0.73-26.12,  $p=0.11$ ). There were no other significant predictors for graft rejection or failure or the composite endpoint as shown in table 2, apart from presence of class IV LN on pre-transplant histology, which was associated with a significant risk of graft rejection/ failure.

Interestingly, longer time on dialysis prior to the transplantation was associated with decreased non-adherence. For every additional month on dialysis non-adherence was reduced by HR 0.96, 95% CI 0.93-0.99,  $p=0.02$ . A receiver operating characteristic (ROC) curve (figure 2), identified that spending more than 25 months on dialysis was more likely to lead to better adherence with sensitivity 0.77, specificity 0.82 and good discrimination with AUC=0.76 supporting the idea that patients who spend more time on dialysis are more likely

to be more adherent, and thus those with less time spent on dialysis prior to transplantation more likely to become non-adherent.

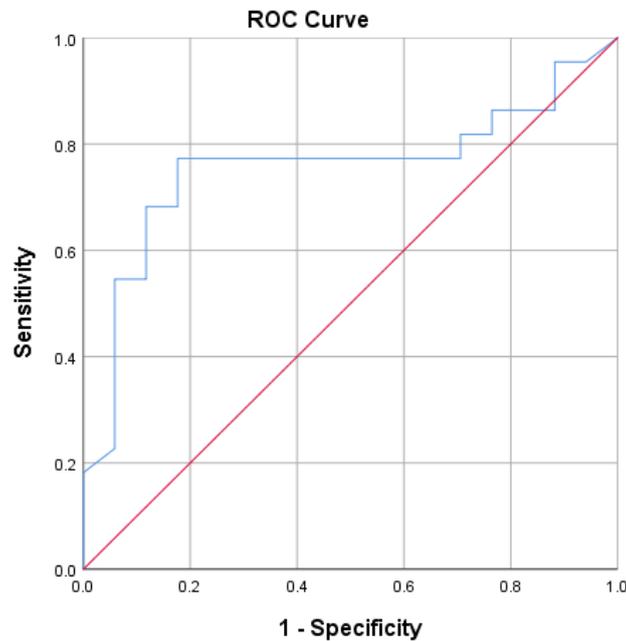


Figure 2: Receiver operating characteristic (ROC) curve indicating supporting that dialysis time of more than 25 months prior to renal transplantation was associated with improved adherence (sensitivity 0.77, specificity 0.82 and good discrimination with AUC=0.76)

## Discussion

In this study we considered the role of adherence to immunosuppressive treatment in patients with lupus nephritis requiring renal transplantation. We documented for the first-time adherence patterns specifically for this cohort of patients and also investigated whether non-adherence was associated with increased risk for graft rejection and/or failure. Our results confirmed that more than 2/5 of our patients with lupus nephritis, even after

renal transplantation, were considered to be non-adherent, either based on medical record evidence or biochemically based on drug level testing.

What is particularly noteworthy, is that once a concern about non-adherence was documented either in the medical notes or as evidenced with biochemical assays, there was a trend to more than a four-fold higher risk of graft rejection, indicating that poor adherence could have potentially significant adverse effects.

As this was an observational retrospective study, it was not possible to investigate causality leading to non-adherence. However, our results raise the strong possibility that patients who spend more time on dialysis are, in fact, more adherent to medication following transplantation. This is an important novel finding, as it may suggest that the time spent on dialysis has an indirect effect in encouraging better adherence post-transplant, perhaps because patients are more motivated to avoid returning to dialysis. With an increasing number of pre-emptive transplantation<sup>6,13</sup> it is possible that non-adherence could also increase and therefore the clinicians and other health care professionals should be aware and ever vigilant in recognizing this. We have recently shown that increasing time on dialysis prior to rTp adversely affects prognosis specifically in lupus patients<sup>14</sup>, supporting previous literature in patients with renal disease of mixed aetiology receiving rTp<sup>15</sup> and therefore minimising the time on dialysis should remain the aim. However, particular attention should be paid to the patients who spent little or no time on dialysis to ensure that non-adherence does not compromise the beneficial effects of early transplantation.

### *Limitations*

Although we included patients from two large hospitals in London over a four-decade period, we were only able to identify 40 eligible transplanted patients from an original cohort of 361 patients. This number although is modest is in line, or larger, than other similar published studies of LN<sup>16,17</sup>. Our study was retrospective, however we endeavoured to avoid any bias by only considering strong pre-defined surrogates for non-adherence, such as clear documentation in the notes about poor adherence, or biochemical markers of non-adherence, and a well-defined end-point of graft rejection and failure.

Moreover, we had a mixture of Caucasian, Afro-Caribbean and South Asian patients and therefore our study results cannot be extrapolated to other populations. In view of this and also the relatively modest numbers in this study, we might have been underpowered to detect small but significant differences specific to individual ethnicity. As we focused our research only in the LN renal transplant patients, we are not able to comment about whether adherence in this cohort is higher or lower than the patients remaining on dialysis. In addition, the retrospective nature of the study did not allow us to screen accurately for depression, a factor known to be associated with non-adherence in the general lupus population<sup>18</sup>. Finally, despite one of the longest recorded follow up periods exceeding 422 patient-years we only had 12 patients with graft rejection or failure, which may have impacted on identifying smaller potential associations with the other variables included in this study.

## **Conclusion**

In conclusion, this study with a notably long-term follow up has shown that poor-adherence persists in patients with LN even after renal transplantation. It further shows that poor adherence may be associated with worse renal graft rejection and that shorter periods on

dialysis prior to transplantation might lead to increased non-adherence. This is the first study to support such a conclusion. Further research needs to be undertaken collaboratively in multiple centres to identify the true adverse role of non-adherence in patients with renal transplant due to lupus nephritis. Such studies can also investigate further the factors leading to poor adherence in this cohort of patients.

Identifying patients at risk of non-adherence utilising a combination of methods based on such factors is a key step. More importantly, patients at risk of, or with documented concerns about adherence should be closely followed up with regular biochemical testing, and a purposeful discussion about the likely consequences of non-adherence in the outpatient clinics may be necessary. Finally, enhanced education sessions highlighting the importance of immunosuppressive therapy adherence could be considered for all the lupus patients following renal transplantation but also importantly in anticipation of renal transplantation.

## **Legends**

**Figure 1:** Flow diagram indicating the study population included in this cohort.

**Figure 2:** Receiver operating characteristic (ROC) curve indicating supporting that dialysis time of more than 25 months prior to renal transplantation was associated with improved adherence (sensitivity 0.77, specificity 0.82 and good discrimination with AUC=0.76)

**Table 1:** Patient demographic comparison between adherent and non-adherent groups.

**Table 2:** Logistic regression hazard modelling investigating non-adherence and other potential predictors and graft-failure.

	Adherence n=23	Non-adherence n=17	P value
Sex/ female	20 (87%)	14 (82%)	0.70
Ethnicity			
Caucasian	8	7	0.46
Afro-Caribbean	10	5	
Asian	5	3	
Age at SLE diagnosis	22 ± 9	21 ± 11	0.55
Age at LN	27 ± 8	26 ± 9	0.63
Time on Dialysis	33 (27-79)	17 (10-24)	0.01
DM	2 (9%)	0 (0%)	0.50
HTN	3 (13%)	6 (35%)	0.12
Dyslipidaemia	3 (13%)	1 (6%)	0.62
APLS	2 (9%)	2 (12%)	0.76
CVS	2 (9%)	3 (18%)	0.43
Histology type IV	9 (39%)	6 (35%)	0.55
Donor living	8 (35%)	10 (59%)	0.20
rTp time			
Before year 2000	6 (26%)	2 (15%)	0.41
After year 2000	17 (74%)	15 (88%)	
Age of ESRD	30 ± 9	32 ± 12	0.59
Age at rTp	36 ± 11	34 ± 12	0.57
Graft rejection	2 (9%)	5 (29%)	0.11
Graft failure	5 (22%)	4 (24%)	0.89
Failure or rejection	5 (22%)	7 (41%)	0.21

**Table 1:** Patient demographic comparison between adherent and non-adherent groups.

	<b>Hazard Ratio</b>	<b>95% Confidence Interval</b>	<b>P-value</b>
<b>Gender male</b>			
Rejection	-		
Failure	0.650	0.066- 6.410	0.650
Rejection or Failure	0.418	0.043-4.024	0.450
<b>Ethnicity</b>	0.758	0.333-1.727	0.510
Rejection	0.697	0.268-1.810	0.458
Failure			
Rejection or Failure	0.597	0.263-1.359	0.219
<b>Age at SLE Diagnosis</b>			
Rejection	1.016	0.949-1.089	0.647
Failure	1.064	0.976- 1.160	0.158
Rejection or Failure	1.048	0.970-1.131	0.236
<b>Age at LN</b>			
Rejection	0.979	0.880-1.089	0.696
Failure	1.033	0.943-1.132	0.482
Rejection or Failure	1.021	0.938-1.111	0.627
<b>Age starting dialysis</b>			
Rejection	1.042	0.966-1.123	0.287
Failure	1.052	0.980-1.129	0.165
Rejection or Failure	1.044	0.976-1.116	0.209
<b>Time on dialysis</b>			
Rejection	0.999	0.982-1.016	0.871
Failure	1.001	0.987-1.015	0.860
Rejection or Failure	0.998	0.985-1.012	0.829
<b>DM</b>			
Rejection	-		
Failure	3.333	0.180-61.686	0.419
Rejection or Failure	2.250	0.125-40.656	0.583
<b>HTN</b>			
Rejection	2.500	0.389-16.049	0.334
Failure	1.750	0.296-10.340	0.537
Rejection or Failure	2.090	0.391-11.061	0.390
<b>Dyslipidaemia</b>			
Rejection	1.200	0.101-14.195	0.885
Failure	3.600	0.400-32.366	0.253
Rejection or Failure	2.286	0.266-19.658	0.451
<b>APLS</b>			
Rejection	1.133	0.096-13.440	0.921
Failure	0.889	0.077-13.300	0.925
Rejection or Failure	2.143	0.248-18.498	0.488

CVS history			
Rejection	-		
Failure	2.000	0.256-15.623	0.509
Rejection or Failure	1.238	0.166-9.253	0.835
Histology type IV			
Rejection	-		
Failure	7.000	0.647-75.735	0.109
Rejection or Failure	9.800	0.899- 106.845	0.061
Donor source			
Rejection	1.619	0.309-8.478	0.568
Failure	1.538	0.342-6.928	0.575
Rejection or Failure	1.909	0.477-7.638	0.361
Non-adherence			
Rejection	4.375	0.733-26.116	0.105
Failure	1.108	0.248-4.944	0.893
Rejection or Failure	2.520	0.632-10.054	0.190

**Table 2:** Logistic regression hazard modelling investigating non-adherence and other potential predictors and graft-failure. Where a (-) is present it indicates too few events in that group to allow statistical modelling.

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