

A proteinuria cut-off level of 0.7 g/day after 12 months of treatment best predicts long-term renal outcome in lupus nephritis: data from the *MAINTAIN Nephritis Trial*

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ABSTRACT

Background: Although an early decrease in proteinuria has been correlated with good long-term renal outcome in lupus nephritis (LN), studies aimed at defining a cut-off proteinuria value are missing, except a recent analysis performed on patients randomised in the Euro-Lupus Nephritis Trial, demonstrating that a target value of 0.8 g/day at month 12 optimised sensitivity and specificity for the prediction of good renal outcome. The objective of the current work is to validate this target in another LN study, namely the *MAINTAIN Nephritis Trial (MNT)*.

Methods: Long-term (at least 7 years) renal function data were available for 90 patients randomised in the *MNT*. Receiver operating characteristic curves were built to test the performance of proteinuria measured within the 1st year as short-term predictor of long-term renal outcome. We calculated the positive and negative predictive values (PPV, NPV).

Results: After 12 months of treatment, achievement of a proteinuria <0.7 g/day best predicted good renal outcome, with a sensitivity and a specificity of 71% and 75%, respectively. The PPV was high (94%) but the NPV low (29%). Addition of the requirement of urine red blood cells ≤ 5 /hpf as response criteria at month 12 reduced sensitivity from 71% to 41%.

Conclusions: In this cohort of mainly Caucasian patients suffering from a first episode of LN in most cases, achievement of a proteinuria <0.7 g/day at month 12 best predicts good outcome at 7 years and inclusion of haematuria in the set of criteria at month 12 undermines the sensitivity of early proteinuria decrease for the prediction of good outcome. The robustness of these conclusions stems from the very similar results obtained in two distinct LN cohorts.

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disease manifestation of systemic lupus erythematosus, impacting quality of life and survival.¹ Identification of short-term prognostic factors predictive of poor long-term outcome in lupus nephritis (LN) would be most welcome, especially to fine-tune the intensity and duration of immunosuppressive (IS) therapy. Another compelling reason is to determine optimal end points for clinical trials so that new therapies can be evaluated efficiently and accurately. In this respect, several reports have demonstrated that an early decrease of proteinuria after IS treatment is predictive of a good long-term renal outcome.^{2–5}

Taking advantage of the long-term follow-up data from the *Euro-Lupus Nephritis Trial (ELNT)*, we were able to determine the optimal proteinuria target that maximises sensitivity and specificity for prediction of good long-term renal outcome. Thus, we demonstrated that a proteinuria of <0.8 g/day 12 months after randomisation was the single best predictor of good long-term renal function, with a sensitivity and specificity of 81% and 78%, respectively.⁶

The current analysis is aimed at testing the validity of this proteinuria target in another patient population with LN, taking advantage of the long-term *MAINTAIN Nephritis Trial (MNT)* data set.^{5,7}

SUBJECTS AND METHODS

The *MAINTAIN Nephritis Trial*

The *MNT* is a European multicentre randomised trial comparing azathioprine and mycophenolate mofetil as maintenance IS treatment of LN, after induction with



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INTRODUCTION

Despite significant therapeutic advances, renal involvement remains a threatening

low-dose Euro-Lupus intravenous cyclophosphamide. After long-term follow-up, renal relapse rates were similar in the two arms, as published elsewhere.^{5,7}

Patient selection

One hundred and five patients suffering from LN were included in the *MNT*. For the purpose of this study, we applied the same patient selection as for the corresponding *ELNT* analysis,⁶ in order to make the two cohorts comparable. Thus, 15 *MNT* patients were excluded because serum creatine (sCr) measurement was not available at or after 7 years of follow-up. Of note, patients having achieved end-stage renal disease at any time (n=4; at month 30, month 36, month 41 and month 74) were included in the analysis. On the whole, data from 90 *MNT* patients were studied.

Definition of good long-term renal outcome

Good long-term outcome was defined as sCr ≤ 1.0 mg/dL at least 7 years after entry into the trial, again in accordance with the criteria used for the *ELNT* analysis.⁶ Conversely, patients with sCr >1.0 mg/dL and those who developed end-stage renal disease at any time were considered as having had a poor renal outcome.

Statistical analyses

We built receiver operating characteristics (ROC) curves, through MedCalc, and calculated their area under the curve (AUC; CIs) to test the performance of each proteinuria level measured at month 3, month 6 and month 12 as a predictor of long-term renal outcome. Briefly, ROC curves plot sensitivity (true positive rate) on the y axis against 1-specificity (false positive rate) on the x axis. The point on the curve closest to the upper left-hand corner, identified by the Youden index, corresponds to the cut-off proteinuria value that optimises sensitivity and specificity. The AUC summarises the overall accuracy of a diagnostic parameter. AUC values >0.9 , >0.7 to 0.9 , >0.5 to 0.7 and 0.5 are highly accurate, moderately accurate, low accurate or equal to chance, respectively.

The optimal proteinuria target value at month 12, as defined supra, was used to calculate the positive and negative predictive values (PPV and NPV).

We also calculated the sensitivity, specificity, PPV and NPV with the addition of other clinical variables to proteinuria, including renal function and urinalysis.

RESULTS

Proteinuria levels that optimise sensitivity and specificity for prediction of good long-term renal outcome

We built ROC curves with proteinuria values measured at different time points within the 1st year of treatment in order to identify the target that best predicts good long-term renal outcome. Figure 1 depicts the ROC curves for proteinuria levels achieved at month 3, month 6 and month 12, their AUCs (CIs) and the

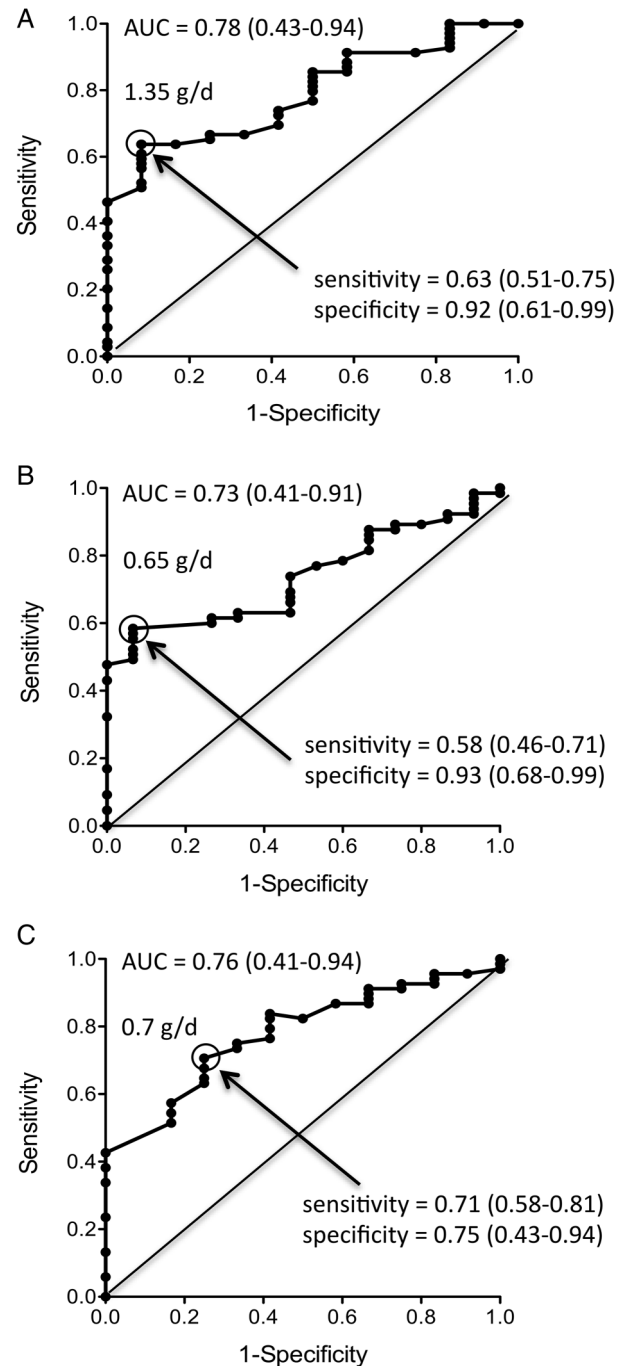


Figure 1 Receiver operating characteristic curves for predictive value of 24 h proteinuria at month 3 (A), month 6 (B) and month 12 (C) of patients randomised in the *MAINTAIN Nephritis Trial*. Sensitivity (true positive rate; y axis) is plotted against 1-specificity (false positive rate; x axis). The proteinuria (g/day) values indicated in the graphs optimise sensitivity and specificity. Figures in brackets are 95% CIs. AUC, area under the curve.

proteinuria cut-off values maximising sensitivity (CIs) and specificity (CIs). After 12 months of treatment, achievement of a proteinuria <0.7 g/day predicted good outcome, with a sensitivity and a specificity of 71% and 75%, respectively.

Table 1 Sensitivity, specificity, PPV and NPV for good long-term renal outcome according to target definition

Target at 12 months	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Proteinuria <0.7 g/day	71 (48/68)	75 (9/12)	94 (48/51)	31 (9/29)
Proteinuria <0.7 g/day and sCr ≤1 mg/dL	63 (43/68)	83 (10/12)	96 (43/45)	29 (10/31)
Proteinuria <0.7 g/day and sCr ≤1 mg/dL and RBC ≤5/hpf	41 (28/68)	67 (8/12)	97 (28/29)	21 (8/38)

Figures in brackets are number of patients: for the sensitivity, patients with good outcome among those achieving the target/total patients with good outcome; for the specificity, patients with poor outcome among those not achieving the target/total patients with poor outcome; for the PPV, patients with good outcome/target achievers; for the NPV, patients with poor outcome/target non-achievers. Of note, only 80 of the 90 patients had proteinuria values available at month 12.

hpf, high power field; NPV, negative predictive value; PPV, positive predictive value; RBC, red blood cells; sCr, serum creatine.

Sensitivity, specificity, PPV and NPV

As indicated in [table 1](#), the PPV for a good long-term renal outcome of achieving a proteinuria <0.7 g/day at 12 months is very high (94%), thereby indicating that proteinuria decrease alone drives long-term renal prognosis. By contrast, the NPV is very low (31%), which means that more than two-thirds of the patients not meeting this target at month 12 will still experience a good long-term renal outcome.

Next, we wondered whether adding renal function and results of urinalyses would modify the sensitivity, specificity, PPV and NPV. As shown in [table 1](#), addition of a normal renal function (sCr ≤1 mg/dL) to the target criteria, did not significantly alter the results. By contrast, requiring urine red blood cells (RBCs) to be ≤5/high power field (hpf), in addition to proteinuria <0.7 g/day and sCr ≤1 mg/dL as a response criteria reduced the sensitivity from 71% to 41%, implying that 59% of the patients who will experience a good long-term renal outcome would not be identified at month 12 if persistent haematuria is part of the target, while only 29% would be missed if proteinuria alone is used as criteria.

Last, we tested whether the NPV of proteinuria <0.7 g/day at month 12 would be higher in patients presenting with lower proteinuria levels at baseline. In these patients, non-achievement of the target should be associated with a poorer prognosis. We selected the mean (3.3 g/day) and the median (2.4 g/day) proteinuria values of the *MNT* cohort as cut-offs. As indicated in [table 2](#), the NPV is indeed higher in patients with a lower baseline proteinuria level.

DISCUSSION

Since permanent renal impairment is mostly a late event in LN, only trials or cohorts with long-term follow-up can unmask patients with poor renal outcome and allow us to test the validity of short-term predictors, such as the kinetics of proteinuria decrease during the 1st year of treatment. The data shown here, computed from the *MNT*, demonstrate (1) that achievement of a proteinuria value <0.7 g/day at month 12 best predicts good renal outcome at 7 years; and (2) that inclusion of microscopic haematuria in the set of outcome criteria at month 12 undermines the sensitivity of early proteinuria decrease for the detection of patients with good outcome.

These observations are consistent with those derived from the *ELNT*. Thus, Dall'era *et al* demonstrated that a cut-off proteinuria value <0.8 g/day at month 12 maximised sensitivity and specificity for the prediction of good renal outcome and that addition of the results of urinalysis negatively impacted early identification of patients with good outcome, with a very comparable drop in sensitivity from 81% to 47%.⁷ We suggest that such a consistency across two distinct trials strengthens the validity of our conclusions.

The finding that haematuria did not contribute as a surrogate for long-term kidney outcomes is not so surprising. In a multicentre trial, it is difficult to ensure that the analysis of the urine sediment is done uniformly. The number of RBCs/hpf depends on the volume in which the pellet of sediment is resuspended. This is not standardised and if the volume is large the cellular elements in the pellet will be diluted and the counts inaccurate. The time of urine collection is important, and how long urine sits before urinalysis may affect the sediment, especially RBC casts. Additionally, there are many reasons for haematuria in a population of mainly young women. The red cells specific for glomerular bleeding, and thus indicative of LN, are dysmorphic and are called acanthocytes. While these cells are enumerated in centres that specialise in glomerular diseases, in clinical trials all RBCs are counted, and these are often eumorphic and from the lower urinary tract. We do not discount the value of urine sediment examination. If urine handling could be standardised and the reader focused on the elements of the urine

Table 2 NPV of a proteinuria <0.7 g/day at 12 months according to baseline proteinuria

Baseline proteinuria (g/day)	NPV (%)
According to mean	
<3.3 (n=48)	44 (7/16)
≥3.3 (n=32)	15 (2/13)
According to median	
<2.4 (n=37)	46 (6/13)
≥2.4 (n=43)	11 (3/16)

Figures in brackets are numbers of patients, in casu poor outcomes/target non-achievers. Of note, only 80 of the 90 patients had proteinuria values available at month 12. NPV, negative predictive value.

that truly indicate glomerular injury, urinalysis may contribute to a surrogate end point of renal response.

The first lesson learned from these analyses is that assessment of microscopic haematuria should not be part of the response criteria used in LN trials, in contrast to the American College of Rheumatology (ACR) recommendations,⁸ more so as interpretation of urinalyses is complicated by delays in sample examination, the use of automated techniques instead of microscopic reading and interference by menstrual-related haematuria.

The second implication deals with treatment options at the bedside after 1 year. Patients meeting the 0.7 g/day proteinuria target at month 12 (ie, 64% of the MNT cohort) can be reassured regarding their final renal outcome, based on the very high PPV (94%). In such patients, glucocorticoid tapering and withdrawal could be considered, based on their well known contribution to damage accrual,^{9 10} although only a controlled trial could test the safety of this proposal in terms of renal relapse rates. On the other hand, treatment decision will be more difficult in patients not achieving the 0.7 g/day target at month 12, due to the low NPV: two-thirds of these patients will still experience a good outcome in the long run. In this respect, the fact that the NPV is twice as high in patients with a low baseline proteinuria compared with those with higher values suggests that a treatment switch might be more appropriate for the former compared with the latter. The kinetics of proteinuria decrease is obviously pivotal in this decision process. Again, only a controlled trial could test the possibility that optimising therapy in partial responders would be beneficial, a hypothesis tested in the RING trial (*R*tuximab in lupus Nephritis with remission as a Goal).

We acknowledge the limitations of our work. Data were acquired in a small patient population. Most subjects were Caucasians (79%) and suffered from their first episode of LN (87%). Further work is needed to improve the NPV which was not ameliorated by the use of a more stringent target, taking into account additional criteria, such as renal function or urinalysis. Yet, the robustness of our conclusions stems from the very similar results obtained in two prospectively followed cohorts.

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Contributors All coauthors have contributed to the study design, data acquisition, data organisation, manuscript writing and reviewing.

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REFERENCES

1. Costenbader KH, Desai A, Alarcón GS, *et al*. Trends in the incidence, demographics, and outcomes of end-stage renal disease due to lupus nephritis in the US from 1995 to 2006. *Arthritis Rheum* 2011;63:1681–8.
2. Houssiau FA, Vasconcelos C, D'Cruz D, *et al*. Early response to immunosuppressive therapy predicts good renal outcome in lupus

- nephritis: lessons from long-term followup of patients in the Euro-Lupus Nephritis Trial. *Arthritis Rheum* 2004;50:3934–40.
3. Houssiau FA, Vasconcelos C, D'Cruz D, *et al*. The 10-year follow-up data of the Euro-Lupus Nephritis Trial comparing low-dose and high-dose intravenous cyclophosphamide. *Ann Rheum Dis* 2010;69:61–4.
 4. Korbet SM, Lewis EJ, Collaborative Study Group. Severe lupus nephritis: the predictive value of a $\geq 50\%$ reduction in proteinuria at 6 months. *Nephrol Dial Transplant* 2013;28:2313–18.
 5. Tamirou F, D'Cruz D, Sangle S, *et al*. Long-term follow-up of the MAINTAIN Nephritis Trial, comparing azathioprine and mycophenolate mofetil as maintenance therapy of lupus nephritis. *Ann Rheum Dis* 2015;■■■.
 6. Dall'Era M, Cisternas MG, Smilek DE, *et al*. Predictors of long-term renal outcome in lupus nephritis trials: lessons learned from the Euro-Lupus Nephritis cohort. *Arthritis Rheumatol* 2015;67:1305–13.
 7. Houssiau FA, D'Cruz D, Sangle S, *et al*. Azathioprine versus mycophenolate mofetil for long-term immunosuppression in lupus nephritis: result from the MAINTAIN Nephritis Trial. *Ann Rheum Dis* 2010;69:2083–9.
 8. Renal Disease Subcommittee of the American College of Rheumatology Ad Hoc Committee on Systemic Lupus Erythematosus Response Criteria. The American College of Rheumatology response criteria for proliferative and membranous renal disease in systemic lupus erythematosus clinical trials. *Arthritis Rheum* 2006;54:421–32.
 9. Gladman DD, Urowitz MB, Rahman P, *et al*. Accrual of organ damage over time in patients with systemic lupus erythematosus. *J Rheumatol* 2003;30:1955–9.
 10. Thamer M, Hernán MA, Zhang Y, *et al*. Prednisone, lupus activity, and permanent organ damage. *J Rheumatol* 2009;36:560–4.