TRAINING BURSARY PROGRAMME REPORT (2019)

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1. What was the motivation to apply for training in this Center? / Main objectives

The main objectives were to conduct a retrospective study investigating the predictive value of repeat kidney biopsies in incident cases of lupus nephritis (LN), and based on these data develop a protocol for a new prospective study of per-protocol repeat kidney biopsy to be conducted within the frame of the Lupus Nephritis Trials Network.

Retrospective study

The role of the repeat kidney biopsy in patients with LN has been discussed rigorously during the last decades, but consensus among researchers and physicians has yet to be established. Before elaborating on the role of the repeat biopsy, it is important to make clear distinctions between different scenarios in which such repeat biopsies can be performed, and how nomenclature has been used in the literature. As discussed in a recent editorial by Anders [1], five different scenarios could be described by the term "repeat biopsy", *i.e.* the per-protocol repeat biopsy at a pre-defined time point for treatment evaluation and new decision of therapy, the partial response repeat biopsy for distinguishing between residual activity and delayed healing and guide treatment accordingly, the flare repeat biopsy, the repeat biopsy to support withdrawal of the immunosuppressive treatment, and the CKD progression repeat biopsy to determine the grade of nephrosclerosis contra treatable active injury. Even if the nomenclature and definitions have not been used uniformly in studies of repeat kidney biopsies, several investigations have shown a discordance between clinical and histological outcome after the initial phase of immunosuppressive therapy for LN. More specifically, most studies reporting results from repeat biopsies have shown that residual renal activity may be evident in repeat biopsies from a considerable proportion of patients who have shown complete clinical responses to treatment, the latter mainly based on the proteinuric outcome [2-6].

The discrepant patterns between clinical and histological data at the time of the repeat kidney biopsy have prompted investigations on the role of the tissue-level information in tailoring treatment, and portending the long-term kidney outcome. While the former question has yet to be addressed in prospective studies, several studies have attempted to address the latter one. Associations between chronic tissue damage in repeat kidney biopsies and long-term impairment of the renal function have been demonstrated in both European and Hispanic LN populations [2, 4]. Nevertheless, this was not confirmed in another study [7], indicating a need for validation. The role of residual activity in repeat kidney biopsies as a marker of the longterm kidney outcome is even less clear. Thus, the idea of a prospective multicentric study of per-protocol repeat kidney biopsies to provide evidence for optimised surveillance and management receives indeed increasing embracement within the LN researcher community [1]. In this direction, within the frame of the SLEuro training programme we aimed at conducting a retrospective investigation of incident cases of proliferative LN, and could demonstrate that different histological components in per-protocol repeat kidney biopsies showed ability to portend

renal relapses and long-term renal function impairment (manuscript submitted for consideration of publication). In this study, high NIH activity index scores in the repeat kidney biopsies were predictive of subsequent relapses, especially activity in the glomerular compartment, and high NIH chronicity index scores were associated with poor long-term renal prognosis, especially chronic damage in the tubulointerstitial compartment.

Prospective study

Accumulating evidence strongly supports the usefulness of repeat kidney biopsies as an integral part of treatment evaluation, including LN patients showing adequate clinical response. Thus, we also aimed at developing the protocol for a new prospective study to be conducted within the frame of the Lupus Nephritis Trials Network. The study will be entitled "Per-protocol **re**peat kidney **bio**psy in incident cases of **lup**us nephritis", or, shortly, **REBIOLUP**.

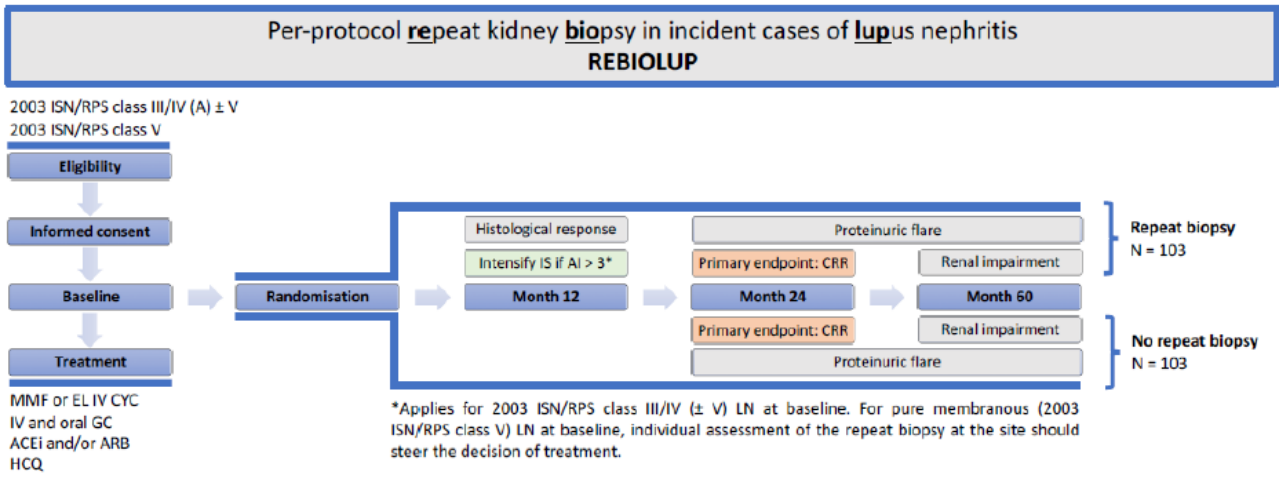

Figure 1. Intended flowchart of the REBIOLUP study.

ISN/RPS: International Society of Nephrology/Renal Pathology Society; MMF: mycophenolate mofetil; EL: Euro-Lupus; IV: intravenous; CYC: cyclophosphamide; GC: glucocorticoids; ACEi: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blockers; HCQ: hydroxychloroquine; IS: immunosuppression; AI: activity index; CRR: complete renal response; LN: lupus nephritis.

The objectives of the project will be:

- to determine the percentage of LN patients in pathological remission after 12 months of standard of care immunosuppression;
- correlate histological and immunological (based on immune deposits) response to therapy with clinical response; and
- evaluate whether therapeutic decisions steered by the results of a per-protocol repeat kidney biopsy improve renal outcomes compared with a matched control group of patients who will not undergo repeat kidney biopsy.

The intended flowchart of the REBIOLUP study is graphically represented in Figure 1. In brief, patients with an incident biopsy-proven proliferative or membranous LN, or combinations thereof, selected to be initiated at standard of care immunosuppressive therapy with either mycophenolate mofetil or intravenous cyclophosphamide according to the Euro-Lupus regimen [8] (combined with glucocorticoids and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers in both cases) will be eligible to be enrolled in the study.

At baseline, patients will be randomised 1:1 to either undergo or not undergo a per-protocol repeat kidney biopsy at month 12 from baseline. In patients with 2003 ISN/RPS class III/IV (±V) at baseline and an NIH activity index score > 3 (cut-off based on retrospective unpublished data) in the repeat

kidney biopsy, the immunosuppressive therapy will be intensified based on the physician's and patient's shared decision. In patients with pure membranous (2003 ISN/RPS class V) LN at baseline, individual assessment of the repeat biopsy will steer the decision of treatment, based on *e.g.* evaluation of immune deposits in electron microscopy or spike formation.
Results from this study, including centralised evaluation of electron microscopy in baseline and repeat kidney biopsies, are anticipated to generate data on how to evaluate response to therapy in pure membranous LN, as well as the value of the information retrieved from repeat kidney biopsies in portending long-term renal prognosis. Patients who have not undergone a repeat biopsy will be treated according to standard clinical parameters, and, finally, percentages of complete renal response at month 24 and renal impairment at month 60 will be compared between the two study arms.

2. How the objectives were fulfilled by thetraining? / Description of activities
My activities included the following:
- Auscultation at the connective tissue disease (CTD) outpatient clinic of the Saint-Luc University Hospital in Brussels, Belgium. This gave me the opportunity to familiarise with an outpatient model that was different to what I am used to, exchange personal experience with local colleagues' experience, and learn new things. Several elements I will be able to apply at my home department.
- Search of the medical charts for retrieving clinical information needed to perform the retrospective study, which in turn supported the development of the protocol for the new prospective multicentric study.
- Study conduct with daily feedback on the progress of the methods used, the results, and the manuscript draft. This was an amazing opportunity that fuelled expeditious progress of the study, which currently is submitted for consideration of publication in a scientific journal.
- Protocol development for a new prospective study with daily feedback, including telephone conferences with collaborators at other centres within Europe and the United States (members of the Lupus Nephritis Trials Network).
- We also summarised current knowledge on outcome prediction in LN in a review to be submitted for consideration of publication in a scientific journal. The manuscript draft is ready and is expected to be submitted by the end of January 2020.

3. What are the main opportunities / strengths this center offers for future applicants?
The main strengths of the centre can be summarised to the following:
- Friendly climate within researchers and medical and paramedical staff.
- Daily feedback by the host Professor Frédéric Houssiau and close collaboration with MD PhD Farah Tamirou.
- Participation in discussion, also outside the scope of the intended project.
- International recognition of the centre and the research conducted there within LN.

4. Practical advice for future applicants to the SLEuro training bursary
Research is a matter of brilliant ideas, persistence and collaboration. I would advise future applicants to take initiatives, bring their own ideas to discussion, be ready to argue for them, and be brave while revising them.
The applicants should also be ready for focused work. The intended outcome has to be reached within a specific time frame.
I would also advice future applicants to be perceptive, and keep a positive attitude to everything that is new. This programme provides a unique opportunity for experience exchange, and career development. Take advantage of this opportunity, and treat it well!
Finally, make sure you have water resistant equipment in your luggage. And don't forget to also have some fun.

5. References

1. Anders HJ. Re-biopsy in lupus nephritis. Ann Transl Med 2018;6:S41.

2. Zickert A, Sundelin B, Svenungsson E, et al. Role of early repeated renal biopsies in lupus nephritis. Lupus Sci Med 2014;1:e000018.

3. De Rosa M, Azzato F, Toblli JE, et al. A prospective observational cohort study highlights kidney biopsy findings of lupus nephritis patients in remission who flare following withdrawal of maintenance therapy. Kidney Int 2018;94:788-94.

4. Malvar A, Pirruccio P, Alberton V, et al. Histologic versus clinical remission in proliferative lupus nephritis. Nephrol Dial Transplant 2017;32:1338-44.

5. Pineiro GJ, Arrizabalaga P, Sole M, et al. Repeated Renal Biopsy - A Predictive Tool to Assess the Probability of Renal Flare in Lupus Nephritis. Am J Nephrol 2016;44:439-46.

6. Arends S, Grootscholten C, Derksen RH, et al. Long-term follow-up of a randomised controlled trial of azathioprine/methylprednisolone versus cyclophosphamide in patients with proliferative lupus nephritis. Ann Rheum Dis 2012;71:966-73.

7. Hill GS, Delahousse M, Nochy D, et al. Predictive power of the second renal biopsy in lupus nephritis: significance of macrophages. Kidney Int 2001;59:304-16.

8. 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;46:2121-31.

I would like to express my gratitude to my respected collaborators Professor Frédéric Houssiau and Doctor Farah Tamirou, who took care of me during my stay. Professor Houssiau and Doctor Tamirou are not only excellent collaborators, but also warm people. They made my stay feel like home. Fortunately, we have developed strong bonds, and will meet again soon at a regular basis. Thank you so much for everything! I would also like to thank SLEuro and my home institute for the opportunity, as well as Professor Bernard Lauwerys, head of the Rheumatology Unit at the Sain-Luc University Hospital, and all medical staff for creating such a wonderful collaborative environment.