ANGIOTENSIN-II RECEPTOR ANTIBODIES BLOCKADE WITH LOSARTAN IN PATIENTS WITH LUPUS NEPHRITIS

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1. STUDY INVESTIGATORS

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2. INTRODUCTION

2.1 Systemic lupus erythematosus and atherosclerosis

Systemic lupus erythematosus (SLE) is an autoinflammatory multiorganic disease with a wide range of clinical manifestations and complications (1). Furthermore, cardiovascular disease constitutes the main cause of death in the world. Atherosclerosis, its characteristic manifestation, develops prematurely in patients with inflammatory diseases, including SLE (2). Patients with SLE have a risk of atherosclerosis 6 times higher than the general population. Likewise, cardiovascular morbidity and mortality is significantly higher in SLE patients as compared to general population (3,4).

The pathophysiology of cardiovascular disease in SLE patients has been linked to the interaction between traditional risk factors (smoking, diabetes, hypertension, dyslipidemia, etc), diseases-specific factors and chronic inflammation-related factors (5,6).

The exact mechanisms that promote atherosclerosis development in SLE are unknown. Recent findings suggest that such mechanisms may obey to a combination of several auto-antibodies, inflammatory activation of the endothelium, dysfunctional lipid assembling, traditional risk factors and negative effects of immunosuppressive drugs (7,8).

2.2 Atherosclerosis damage assessment

There are two accepted techniques to evaluate atherosclerosis damage in grand vessels: coronary artery tomography and carotid arteries ultrasound. Carotid intima-media thickness (CIMT) is evaluated by B-mode or M-mode Doppler ultrasound. CIMT has been used for subclinical atherosclerosis evaluation and follow-up, even in patients with SLE (9,10,11). Besides CIMT, carotid plaque measurement has been recommended for cardiovascular disease epidemiological studies, and has even been referred as an acceptable cardiovascular event predictor in some studies (12,13).

2.3 Subclinical atherosclerosis in lupus nephropathy

Several studies have compared subclinical atherosclerosis prevalence among SLE patients compared to the general population. In a recent metaanalysis (14), including 80 studies (71 evaluating CIMT and 44 carotid plaques), higher CIMT was found and a higher prevalence of carotid plaques in SLE patients. Metaregression analysis showed that traditional cardiovascular risk factors and steroid use were the most important factors associating SLE and carotid plaques. In the subgroup of lupus nephropathy patients, there was higher CIMT compared to patients with SLE without renal manifestations (14).

It is unknown why the prevalence of atherosclerosis is higher in patients with lupus nephropathy. Among proposed mechanisms, it has been described a higher level of vascular endothelium growing factor (VEGF) in this subgroup of patients (15).

2.4 Vascular lesions in lupus nephropathy renal biopsies

Renal biopsies constitute the gold standard for lupus nephropathy diagnosis. Based in the glomerular, interstitial and vascular compartment findings, the renal pathologist report the findings according to the classification developed by the International Society of Nephrology and the Renal Pathology Society (ISN/RPS) (16).

In recent years, focus has been given to the vascular compartment. This includes medium-size and small-size vessels (17,18). Vascular lesions have been reported in 27 to 82% of renal biopsies, being the arteriolar sclerosis the most common among them. In our center,

we have shown, that those patients without vascular lesions have higher possibilities to respond to immunosuppressive treatment when compared to those with arteriolar sclerosis (19). Furthermore, arteriolar sclerosis was found in 42% of renal biopsies, being correlated with worse prognosis in univariate analyses and showing a moderate correlation with chronic damage indexes (interstitial fibrosis, tubular atrophy) (20).

It is currently unknown if there is any association between arteriolar sclerosis findings in the renal biopsy and great vessel atherosclerosis findings.

2.5 Angiotensin-II type 1 receptor antibodies (ATR1-Ab)

Angiotensin-II type 1 receptor is present in endothelial cells and smooth muscle cells in the vessels. After binding to angiotensin-II, through second messengers, this receptor contributes to regulation of body fluid composition and arterial pressure (21).

ATR1-Ab are agonist antibodies, they do not fix complement, and promote hypertension development by overactivating AT1R. Furthermore, AT1R-Ab may induce microvascular inflammation and activation of the coagulation pathway through the stimulation of B-cells nuclear factor kappa (NF-kB) and the expression of tissue factor from endothelial cells. At the end, this manifests as endarteritic lesions, fibrinoid necrosis and microthrombi.

In 1999, *Wallukat et al* described the presence of this agonistic antibodies in the serum of preeclamptic patients, being responsible for an elevation of arterial pressure. These antibodies disappear after the end of pregnancy (22).

In 2005, *Dragun et al*, associated these antibodies with acute allograft rejection (23). The antibodies were studied because such patients presented with malignant arterial hypertension resembling arterial hypertension observed in preeclamptic patients. Antibody removal by plasmapheresis and/or selective blockade of AT1R with losartan, incremented allograft survival (23,24).

AT1R-Ab may also contribute to oxygen free radicals, pro-inflammatory response and NADPH oxidase NFkB-dependent activation (23,25,26). These antibodies may stimulate

the expression of adhesion molecules and tissue factor production in the endothelium (27-29). All these effects may be related to arterial sclerosis pathophysiology.

Dechend et al (30) have found similar arterial sclerosis lesions in spiral arteries from placentas in AT1R-Ab murine preeclampsia models. Li et al (31), have administrated a peptide from the receptor to stimulate the production of AT1R-ab in ApoE-/- rabbits. After sensitization, these rabbits overexpress inflammatory mediators such as C-reactive protein, tumoral nuclear factor alpha, NF-kB and oxidative stress mediators (H2O2). These animals develop atherosclerosis in the aorta that is reversible by the AT1R blockade with valsartan.

To date, the only study evaluating the presence of AT1R-Ab in SLE patients showed a prevalence of 66.3% in patients with lupus nephropathy in comparison to 9.6% in normal controls without SLE (32). The prevalence of these antibodies in lupus nephropathy patients without immunosuppressive treatment was 76.1% compared to 27.8% for those under immunosuppression, suggesting that immunosuppressive treatment modifies antibody levels. Arterial pressure was significantly higher in patients positive for AT1R-Ab in comparison to those negative to these antibodies (32).

Finally, in a recent study in our center which was focused to the role of AT1R-Ab in renal transplant patients, we found a medium AT1R-ab level of 85.1u/ml in patients with lupus nephritis ESRD compared to 16.3u/ml in patients with ESRD from other etiologies. Those patients positive for AT1R-Ab showed higher grades of arterial sclerosis in renal biopsies compared to those AT1R-Ab negative (Alberu J – unpublished data).

3. JUSTIFICATION

Atherosclerosis is the first cause of death in the world. Accelerated atherosclerosis has been noted in inflammatory diseases such as SLE. This increments morbidity and mortality among these patients. Some groups have advocated an autoimmune component underlying hypertension (33,34).

We currently know that renal damage and progression to end-stage renal disease produces morbidity and mortality in SKE patients. The presence of arterial sclerosis in renal biopsies has been associated with lower response to treatment (19) and a lower renal survival (20).

Therefore, research of pathophysiological mechanisms that guide to vascular damage both in great vessels (atherosclerosis) and medium and small vessels (arteriolar sclerosis) may contribute to enhance response to treatment and prognosis in patients with inflammatory diseases.

AT1R-Ab constitute a suggested autoimmune damage mechanism that has been studied in diseases accompanied by hypertension such as preeclampsia and allograft rejection.

This study will describe the prevalence of AT1R-Ab in patients with lupus nephropathy and their association with vascular damage in great and small vessels. Importantly, if a pathogenic mechanism is demonstrated, treatment with angiotensin receptor antagonists could reverse this pathogenic effect.

4. HYPOTHESIS

Atherosclerosis progression measured by carotid intima-media thickness will have a slower progression in AT1R-Ab positive patients treated with losartan compared to those treated with enalapril

5. OBJECTIVES

Primary

Compare the rate of carotid intima-media thickness progression in AT1R-Ab positive lupus nephritis patients treated with losartan compared to those treated with enalapril.

Secondary

Compare the response to therapy rate between AT1R-Ab positive lupus nephritis patients treated with losartan compared to those treated with enalapril

Compare the 24-hour blood pressure control between AT1R-Ab positive lupus nephritis patients treated with losartan compared to those treated with enalapril

6. METHODOLOGY

6.1 General design

This is an open label randomized clinical trial, with two parallel group comparison.

Every patient with SLE diagnosis scheduled for a renal biopsy procedure will be invited to participate. After consent form signing, a full medical evaluation will be performed which includes cardiovascular risk factors, SLE previous history and treatment, physical examination, ambulatory blood pressure measurement (ABPM). We will collect blood and urine samples.

Before the renal biopsy procedure, a mode-B carotid Doppler ultrasound will be performed to determine CMIT in three points (common carotid artery, carotid artery bulb and internal carotid artery) and to search for plaques.

In the renal biopsy tissue, arterial sclerosis will be quantified in every vessel under the Masson staining and will be expressed as arterial sclerosis percentage.

Plasma will be evaluated for the presence of angiotensin-II type 1 receptor antibodies. Those patients positive for antibodies (>17UI/ml) will be randomized to receive treatment with either enalapril 10mgs QD or losartan 50mgs QD as adjunctive therapy to the immunosuppressive induction to remission therapy.

Patients will be randomized and stratified according to immunosuppressive treatment (mycophenolate mofetil of cyclophosphamide).

Response to treatment will be evaluated monthly for the first 6 months and then every 3rd month for 12 months. Each visit will include the studies mentioned in Supplementary Table 1, these include 24-hour proteinuria, serum creatinine and serologies. A physical examination and adherence questionnary will be applied at 12, 24 and 52 weeks.

At week 52th, a second mode-B Doppler ultrasound and ABPM will be performed. Renal vascular lesion progression will be evaluated in a protocolized 12-month renal biopsy.

6.2 Length of the study

52 weeks.

6.3. Patient selection

6.3.1. Number of patients

We will invite to participate to every patient programmed for renal biopsy between September 2017 and June 2018. According to our local registry, approximately 80 percutaneous renal biopsies are performed in SLE patients every year. The reported prevalence of CIMT abnormalities and plaques documented by carotid ultrasound is close to 30%.

6.3.2 Inclusion criteria

- Patient programmed for percutaneous renal biopsy
- Signed consent form before any procedure
- Adult (>16 years and <50 years) male or female
- At least 4 ACR criteria for systemic lupus erythematosus diagnosis
- Histopathological diagnosis of class III, IV, V lupus nephritis without comorbid findings in the biopsy
- Less than 6 weeks with the use of prednisone >1mg/kg
- 24 hour urine protein to creatinine ratio > 1.5g/g

6.3.3 Exclusion criteria

- Not willing to sign consent form
- Comorbid diseases associated with proteinuria such as type 2 diabetes with diabetic retinopathy or suspicion of another glomerulopathy.
- Comorbid disease with previous documented atherosclerosis such as systemic hypertension >5years or diabetes with micro/macrovascular complications
- Previous diagnosis of resistant arterial hypertension
- Mycophenolate mofetil >2g for more than 6 weeks
- Cyclophosphamide administration within 3 months
- Use of any biologic therapy within 6 months
- Active pregnancy or unwilling to use contraception during the study
- Contraindication to any of the studied drugs
- Patient participating in another research study

6.3.4. Elimination criteria

- Bad window or methodological problems to obtain CIMT measurements by Doppler ultrasound
- Insufficient renal biopsy tissue to evaluate vascular lesions
- Presence of a second glomerulopathy in renal biopsy
- Negative AT1R-Ab result

6.3.5 Consent retirement

Patients may retire their consent at any time and without further explanations.

6.3.7 Outcome definitions

Outcome definitions can be appreciated in Table 1.

Outcome	Definition
Carotid intima-media thickness progression	Change in the CIMT measured by mode-B Doppler ultrasound between baseline and 12-month biopsies
Carotid plaques	Defined as present or absent in Doppler ultrasound
Response to treatment	Diminishment of urine protein to creatinine ratio to less than 3g/g if baseline uPCR nephrotic or 50% diminishment if baseline uPCR subnephrotic
Complete remission	Defined by a urine protein to creatinine index less than 0.5g/g
Time to response to treatment	Months from immunosuppression start to response to treatment
Time to complete remission	Months from immunosuppression start to complete remission

7. Laboratory studies across the study

7.1 Sample management and storage

Before the renal biopsy procedure two 5ml blood tubes and one 5ml urine tube will be stored in Eppendorf tubes at -70°C.

7.2 Angiotensin-II Receptor 1 antibodies measurement

The serum AT1R-Ab levels will be quantified by ELISA (CellTre GmbH, Luckenwalde, Germany) in samples at day 0, week 12, week 24 and week 52.

7.3 Carotid Doppler ultrasound

A baseline carotid ultrasound will be performed before the diagnostic percutaneous renal biopsy and at the week 52 of follow-up.

With the patient in supine position and with the neck rotated to the opposite side, images from the common carotid, carotid bulb and internal carotid artery anterior and posterior walls will be obtained in mode B. An abnormal CIMT will be defined as that over 0.8mm (41).

7.4 Histopathological analysis of percutaneous renal biopsy

Renal biopsies will be fixated with 4% formol for light microscopy analysis. Sequential 3-um sections will be stained with hematoxylin-eosin, Schiff periodic acid, silver metenamine and Masson's thricrome.

Activity and chronicity scores will be determined as described by Austin et al.

Arteriolar sclerosis will be defined as a fibrous thickening of the intimal without necrosis, proliferation or thrombosis. Quantification will be performed by morphometry considering the elastic media circumference as 100% and then defining the percentage of vessel occlusion (43). Values will be expressed in a 0 to 100.

7.5 Laboratory studies

As a routine, every patient is evaluated with complete blood count, coagulation tests, chemistry tests, urine tests including 24h urine to protein ratio, double-strand DNA antibodies, complement C3 and C4 serum levels. These test are repeated every 3 months.

AT1R-antibodies will be evaluated at baseline and week 12, 24 and 52.

8. Treatment Assignment

All patients with proliferative lupus nephritis receive treatment with either ACE inhibitors or angiotensin receptor antagonists. For those patients who are willing to participate, they will be randomized to receive losartan 50mgs BID or enalapril 10mgs BID for 52 weeks as an adjunctive treatment to immunosuppression. Randomization will be performed by blocks according to induction treatment (mycophenolate mofetil or cyclophosphamide) with the software available in http://randomization.com

9. Concomitant immunosuppression

At present, there are two first-line treatments for lupus nephropathy: mycophenolate mofetil at dose higher than 2g/day and IV cyclophosphamide administered according to the modified NIH scheme.

Immunosuppression assignment will be performed by the treating physician and treatment will be standardized to 6 monthly IV cyclophosphamide boluses or mycophenolate mofetil at dose higher than 2g/day.

Prednisone dose will be administered as described in Table 2.

Time	Dose
Day 0	60mg
Week 6 ± 2	40mg
Week 8 ± 2	30mg
Week 10 ± 2	25mg
Week 12 ± 2	20mg
Week 14 ± 2	15mg
Week 16 ± 2	10mg
Week 18 ± 2	7.5mg
Week 20 ± 2	5mg
Week 24 ± 2	Less than 5mg

9.1 Steroid rescue therapy

In case of extrarenal SLE activity and if decided by the treatment physician, steroid dose may deviate from tapering protocol or be increased at any time during the study. This should be documented in patient's file.

10. Treatment Adherence

Patients will be followed-up monthly for the first 6 months and then every 3 months. At each visit, treatment drugs and dose will be registered. In the visits at week 12, 24 and 52, the questionnaire of Morisky and Green will be applied (44).

11. Risk and Precautions

11.1 Percutaneous renal biopsy

This study will not influence scheduling of percutaneous renal biopsies. According to our local statistics, major complications may happen in less than 3% of the procedures and in less than 1% of those patients without risk factors for bleeding complications (45,46).

11.2 Laboratory studies

Blood will be drawn at 4 times obtaining no more than 10cc/ea. Risk from this procedure are local hematoma, infection with very low incidence.

11.3 Carotid Doppler ultrasound

It is a non-invasive procedure without associated risks.

12. Statistical Analysis

All data will be analyzed by SPSS 20.0 and GraphPad Prism software.

Estimated sample will be 40 subjects randomized to losartan or enalapril treatment and stratified by induction treatment.

Considering a 20% difference in the progression of carotid intima media thickness between both groups, with an alpha error of 5%, the power would be 92.9% and 98.8% with 7 and 10 subjects per group respectively.

12.3 Statistical analysis

Data will be evaluated by means of the Kolmogorov-Smirnov test and descriptive statistics will be described accordingly. Comparisons will be made by means of t-test or Mann-Whitney's U according to variable distribution. Pearson coefficients will be calculated to estimate association between log-transformed AT1R-ab levels, CIMT and arteriolar sclerosis percentage in renal vessels.

Kaplan-Meier curves will be plotted for response to treatment and time to response to treatment analyses. Response to treatment prognostic factors will be determined by Cox-regression analysis.

13. Benefits and Risk of the study

13.1 Discomfort associated with the study

Every patient will be performed two ABPM, two Doppler carotid ultrasound and a total of four blood and urine samples will be drawn.

13.2 Potential risks

Venipuncture associated risks are hematoma, bleeding, infection.

ABPM can be associated with a local hematoma in the site of the cuff.

Treatment drugs can be associated with hyperkalemia, acute renal failure, cuff (ACE inhibitors).

Any effect considered as “probable” or “possible” secondary to the drugs of the study will be evaluated by the principal investigator.

13.3 Direct benefits

No direct benefits are expected from phase 1. For phase 2, a benefit in arterial sclerosis progression is expected for those patients treated with losartan.

13.4 Indirect benefits

No indirect benefits to the patient are expected.

14. Procedure Description

a) Ambulatory blood-pressure monitoring (ABPM)

This study will be performed with our Department blood monitors (Welch Allyn) before the renal biopsy.

b) Hospitalization and percutaneous renal biopsy

This study includes histopathological analysis of renal tissue. The renal percutaneous renal biopsy or its complications are not procedures of the study. Indications and complications will be managed by the treatment physician.

c) Carotid Doppler ultrasound

This study will be performed previous to the performance of the renal biopsy at the Imagenology department by a single experienced sonologist who is an associated investigator of this study. The follow-up ultrasound will be performed at week 52.

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