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Original Article

ORIGINAL ARTICLE

Randomized clinical study to evaluate the effect of personalized therapy on patients with immunoglobulin A nephropathy

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ABSTRACT

Background. Randomized controlled trials (RCTs) have been conducted, stratifying idiopathic immunoglobulin A nephropathy (IgAN) patients based on the laboratory findings [serum creatinine, estimated glomerular filtration rate (eGFR) and daily proteinuria]. In contrast, data from kidney biopsy have been used only for clinical diagnosis. Therefore, IgAN patients with active or chronic renal lesions have been receiving the same therapy in experimental and control arms of randomized clinical trials (RCTs).

Methods. Our clinical study of IgAN (CLIgAN) is a multicentre, prospective, controlled and open-label RCT based on patients' stratification at the time of their kidney biopsy. We will consider, first, the type of renal lesions, followed by serum creatinine values, eGFR and proteinuria. Primary and secondary endpoints will be monitored. Then, we will determine whether personalized therapy can slow the decline of renal function and delay end-stage kidney disease.

Results. We will enrol 132 IgAN patients with active renal lesions (66 patients per arm) in the first RCT (ACIgAN). They will receive corticosteroids combined with renin–angiotensin system blockers (RASBs) or only RASBs. A total of 294 IgAN patients with chronic or moderate renal lesions at high or very high risk of chronic kidney disease (147 patients per arm) will be enrolled in the second RCT (CHRONIgAN), in which they will receive dapagliflozin, a sodium–glucose cotransporter 2 inhibitor, combined with RASBs, or RASBs alone.

Conclusion. Using this approach, we hypothesize that patients could receive personalized therapy based on renal lesions to ensure that the right drug gets to the right patient at the right time.

Keywords: corticosteroids, dapagliflozin, immunoglobulin A nephropathy, kidney biopsy, randomized controlled trial, renin–angiotensin system blockers

INTRODUCTION

Idiopathic immunoglobulin A nephropathy (IgAN) is the most common biopsy-proven glomerulonephritis in the world. It is more prevalent in Asia than in Europe and the USA [1]. Worldwide, approximately 40% of IgAN patients reach end-stage kidney disease (ESKD) within 20 years of their kidney biopsy [2, 3].

The KDIGO 2012 guidelines suggest different therapeutic approaches based on the clinical setting [4]. Patients with

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proteinuria >0.5 g/day, normal or reduced estimated glomerular filtration rate (eGFR), and normal or high blood pressure may benefit from continuous supportive therapy [renin–angiotensin system blockers (RASBs)] when proteinuria lowers to <1 g/day and eGFR remains stable. When proteinuria is >1g/day and eGFR (normal at baseline) declines to >50 mL/min/1.73 m^2, patients may benefit from corticosteroids combined with RASBs for 6 months after supportive therapy for 3–6 months. When eGFR is <30 mL/min or between 30 and 50 mL/min/1.73 m^2, only RASBs are recommended, with no immunosuppression. These indications have been confirmed in the recent edition of the KDIGO 2021 guidelines [5], which state as the first step to score kidney biopsy according to the Oxford classification [6–8]. However, as reported by the KDIGO guidelines, there is insufficient evidence to support the use of this classification in determining whether immunosuppression should be commenced in IgAN. Moreover, there is insufficient evidence to base treatment decisions on the presence and number of crescents in the kidney biopsy. However, the KDIGO guidelines do not consider the presence of active (endocapillary and extracapillary lesions) and chronic (tubulointerstitial lesions) renal lesions at the time of the kidney biopsy for therapeutic choice.

Recently, Yang *et al.* [9] analysed the response of renal lesions to corticosteroids in a systematic review and meta-analysis. They concluded that IgAN patients with active renal lesions (endothelial proliferations, E1) responded better to corticosteroids than patients with tubulointerstitial lesions (T1,2). The extracapillary lesions (C) were not considered in the analysis because the evidence for these lesions was limited. However, another systematic review and meta-analysis [10] evaluated the association between the C lesions and kidney failure. That review concluded that the crescent's formation represented a prognostic factor associated with the progression of kidney damage. Therefore, this type of lesion must be considered early in the therapeutic approach.

Recently, oral sodium–glucose cotransporter 2 inhibitors (SGLT2i) were administered in patients with diabetic nephropathy type 2 and in other participants with chronic kidney disease (CKD); some of them were affected by IgAN [11–14]. The effect of SGLT2i was compared with a placebo. All patients received RASB therapy. Patients with CKD who received SGLT2i had a significantly lower risk of a composite endpoint (sustained decline of eGFR of at least 50%, ESKD, or death from renal or cardiovascular causes), independent of the presence or absence of diabetes [14, 15].

Based on those data, our clinical study in IgAN patients (CLIgAN) will consider, first, the type of renal lesions and then the laboratory findings because, combining the MEST-C [M (mesangial cellularity); E (endocapillary proliferation); S (segmental glomerulosclerosis), T (tubular atrophy/interstitial fibrosis); C (crescents)] score of the Oxford classification with cross-sectional clinical data at biopsy, we will provide earlier risk prediction in IgAN [16].

We plan to evaluate (i) the effect of corticosteroids combined with RASBs versus RASBs alone in IgAN patients with active renal lesions and (ii) the effect of SGLT2i (dapagliflozin) combined with RASBs versus RASBs alone in patients with chronic or moderate renal lesions (CHRONIgAN) at high or very high risk of CKD.

MATERIALS AND METHODS

Study design and intervention

We have designed a prospective, multicentre, open-label study, illustrated in Figure 1, which includes two randomized controlled trials (RCTs) based on the kidney biopsy report.

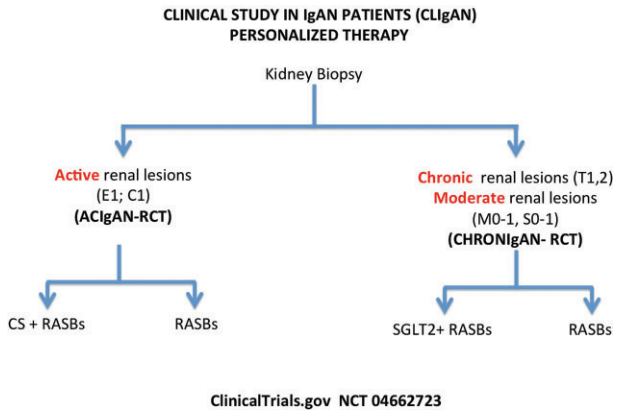

FIGURE 1: Schematic representation of the CLIgAN study. IgAN patients will be enrolled into two different RCTs. Patients with active renal lesions (E1 and/or C1) will be randomized to receive CS combined with RASBs versus RASBs alone. Patients with chronic (T1,2) or moderate (M0,1, S0,1, E0, C0, T0) renal lesions will be enrolled to receive SGLT2i (dapagliflozin) combined with RASBs versus RASBs alone. M, mesangial hypercellularity; E, endocapillary hypercellularity; S, segmental glomerulosclerosis; T, tubular atrophy/interstitial fibrosis; C, cellular or fibrocellular crescents; CS, corticosteroids; RASBs, renin–angiotensin system blockers; SGLT2i, sodium–glucose cotranspoter 2 inhibitor.

IgAN patients with active renal lesions (E1 and or C1) (ACIgAN), proteinuria ≥0.5 g/24 h and eGFR ≥30 mL/min/1.73 m^2 will be randomized into two arms to assess the superiority of corticosteroids combined with RASBs (experimental arm) versus RASBs alone (control arm).

IgAN patients with chronic renal lesions (T1,2) (CHRONIgAN) or moderate renal lesions (M0,1, S0,1, E0, C0, T0), proteinuria >0.5 g/24 h and eGFR ≥30 mL/min/1.73 m^2 will be randomized into two arms to assess the superiority of SGLT2i combined with RASBs (experimental arm) versus RASBs alone (control arm).

Figure 2 shows that patients assigned to the corticosteroid group (experimental arm) will receive (pulses) intravenous methylprednisolone succinate (SOLU-Medrol) 500–1000 mg/day for 3 consecutive days followed by oral prednisolone (0.5 mg/kg/body weight) on alternative days until the end of each month for 3 consecutive months. Then, corticosteroids will be gradually tapered every 2 weeks as follows: 20 mg, 10 mg and 5 mg on alternate days until 6 weeks. The dose of SOLU-Medrol will be individualized (15 mg/kg) based on the ideal body weight and administered in a single daily dose intravenously for 30–60 min. Corticosteroids will be administered only in the morning. Participants who will receive RASBs alone (control arm) and will be non-responders to 3 months of optimized supportive therapy will receive corticosteroids combined with RASBs as described in the experimental arm and suggested by the KDIGO guidelines [5]. In presence of proteinuria <0.5 g/day, patients will continue RASB therapy.

Figure 3 shows that IgAN patients with chronic or moderate renal lesions, assigned to the experimental arm, will receive dapagliflozin (10 mg/day) combined with RASBs. The SGLT2i will be administered after a stable dose of RASBs given for at least 4 weeks. Patients of the control arm, who will be non-responders to RASBs alone after 12 months or at other subsequent outpatient visits, will be switched to the experimental arm (dapagliflozin combined with RASBs).

In both RCTs, oral RASBs will be titrated to their maximum anti-proteinuric effect. They will be administered to reduce proteinuria to 0.5 g/24 h or less and to achieve and maintain a systolic and diastolic blood pressure <130 and 80 mmHg [17]. RASBs will be administered twice a day (8 am and 8 pm) to control

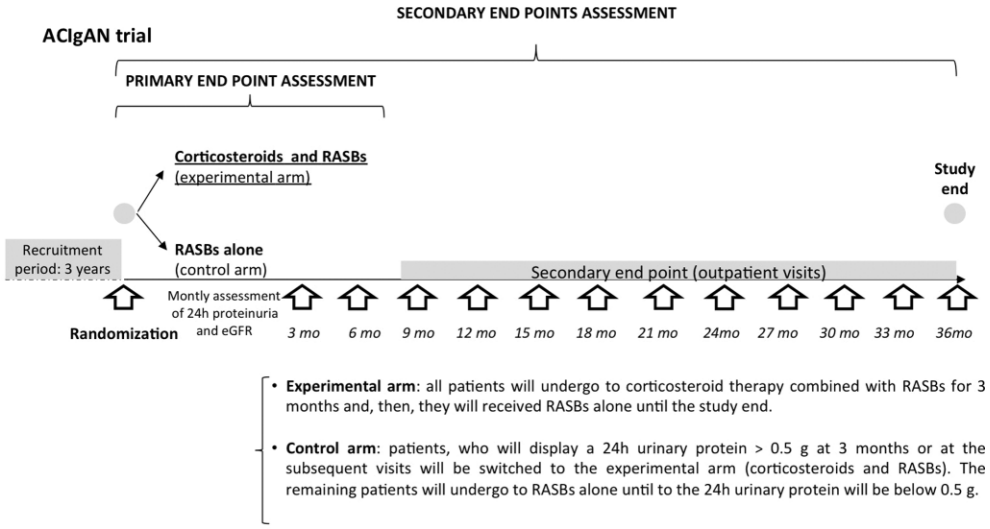

FIGURE 2: ACIgAN trial. Design of the study.

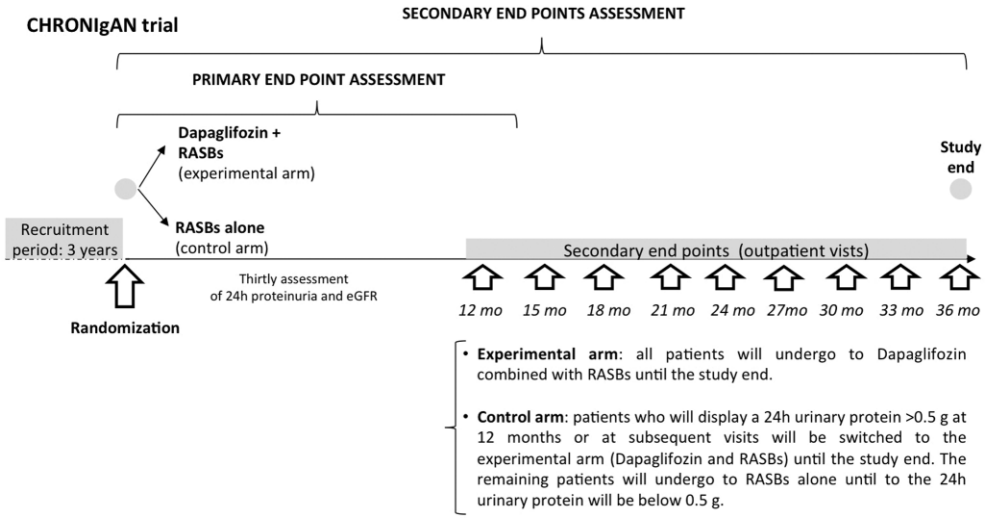

FIGURE 3: CHRONIgAN trial. Design of the study.

blood pressure. Kalaemia will be controlled so as not to exceed 5.5 mEq/L. In presence of hyperkalaemia, drugs lowering potassium will be administered. If necessary, other anti-hypertensive drugs will be administered.

Recruitment and follow-up

The recruitment will start on January 2022 and will be closed by December 2025. Adult biopsy-proven IgAN patients (age 18–75 years) will be eligible to participate in the study. They will be enrolled in European renal units in a time frame of 3 years. Inclusion and exclusion criteria are illustrated in Table 1. During the follow-up, patients with a rapid decrease of eGFR will receive kidney biopsy.

After initial eligibility screening of the clinical data and kidney biopsy report, each patient will receive an explanation of the trial plan. After the signature of the consensus participation, the patient will be enrolled and randomized separately in each trial (allocation 1:1 ratio) via a web-based programme generating random numbers to ensure allocation concealment. Patients with active renal lesions will be randomized by 2 weeks from the kidney biopsy. Patients with chronic or moderate renal lesions at high CKD risk will be randomized by 4 weeks from the kidney biopsy. Stratified randomization will be done by age, sex and kidney biopsy. The follow-up study to measure the outcomes will consist of regular outpatient visits at the prescribed times to collect clinical and laboratory data and information on drug adherence. Before the trial is complete, each participant will receive a final visit. Drop-out criteria during the follow-up include pregnancy, death or withdrawal of consent.

Safety information will be collected for the intention-to-treat population by recording severe adverse events (AEs). Infections, impaired glucose tolerance, weight gain and hypoglycaemia will be monitored during the follow-up. Upon confirmation, the severity of the AEs will be evaluated for the procedures conducted, the outcomes and the relationships to the study drugs.

Table 1. CLIgAN study

Inclusion criteria
- IgAN patients with active renal lesions (E1 and/or C1) will be enrolled in ACIgAN study.
- IgAN patients with chronic (T1,2) or moderate (M1, S1, E0, T0, C0) renal lesions at high or very high CKD risk (24-h proteinuria ≥0.5 g and eGFR ≥30 mL/min/1.73 m^2) will be enrolled in CHRONIgAN study.
Exclusion criteria
- IgAN patients with active renal lesions and kidney biopsy elapsed more than 2 weeks.
- IgAN patients with chronic renal lesions and kidney biopsy elapsed more than 4 weeks.
- IgAN patients with minimal change disease at kidney biopsy and nephrotic syndrome.
- IgAN patients with macrohaematuria and acute renal failure.
- IgAN patients with rapid deterioration of the renal function caused by the presence of extracapillary lesions in more than 25% of glomeruli in the kidney biopsy.
- Patients with secondary IgAN (lupus nephritis, Schönlein–Henoch purpura, liver cirrhosis).
- Superimposed IgAN in a kidney transplant.
- Patients with myocardial infarction or cerebrovascular stroke in the previous 6 months.
- Severe liver diseases, infections, malignancies, pregnancy.
- Uncontrolled diabetes.
- Aseptic necrosis of any bone.
- Any prior immunosuppressive therapy.
- Other conditions that can be exacerbated by corticosteroids.
- Previous adverse side effects to RASBs and SGLT2is.

The CLIgAN study has been designed according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Statement (Supplementary data, Table S1) and to the Statistical Principles for Clinical Trials (ICH Topic E9) edited by European Medicines Agency (EMEA) (Supplementary data, Table S2). The CLIgAN study has been registered in the ClinicalTrials.gov (NCT 04662723).

General measures

Age, body mass index, eradication of infectious foci or concurrent antibiotic therapy to prevent infections or to avoid the transformation of a trivial infection into a severe complication will be considered.

Blood hypertension in participants with CKD is defined when values are >130/80 mmHg or in subjects treated with antihypertensive drugs.

Patients with CKD stages 1–3 will observe the Mediterranean diet combined with reduced intake of animal proteins (0.8 g/kg body weight/day) (Supplementary data). Salt (sodium chloride) intake will be limited to 5.0 g/day [18]. Dietary compliance will be assessed by measuring daily urinary sodium and urea excretion every 3 months.

Patients with dislypidaemia will be treated according to recent guidelines [19]. Allopurinol will be administered in the presence of hyperuricaemia. Non-steroidal anti-inflammatory drugs and other nephrotoxic drugs will be avoided. Cimetidine will not be prescribed because it interferes with serum creatinine measurements. Other gastroprotective drugs will be administered. Physical activity will be observed for 30 min every day, primarily in the morning.

Renal measures

(i) Kidney biopsy, scored according to the Oxford classification [6–8], will be the principal keynote because active renal lesions will be treated with immediate corticosteroid therapy (by 2 weeks from the kidney biopsy) before lesions become chronic. In two RCTs [20, 21], IgAN patients received 6 months of RASBs before their enrolment for corticosteroid therapy. In our opinion, this approach is not appropriate because the active renal lesions evolve in chronic lesions and are non-responsive to corticosteroid therapy after 6 months of RASB therapy. Therefore, the aim of our RCT is early treatment.

The definition of remission or no response of the renal lesions to therapy in published retrospective clinical studies [22–24] is inconsistent. Therefore, high-quality RCTs with a large sample size are necessary to define the response of histological renal lesions to corticosteroids. Moreover, no larger RCT has confirmed that the disease improves when clinical decisions are made quickly in the presence of the histological score.

Kidney biopsy will be analysed by independent renal pathologists, blinded to the study results, using digital histopathologic analysis coupled with machine-learning tools. The report will be based on a fixed layout and structure, covering all aspects of the biopsy in a sequential manner. Two independent pathologists will evaluate the renal lesions by using the Oxford classification (MEST-C scores). If the two pathologists score differently, a third pathologist will score the biopsy and the results will be discussed among the pathologists to reach a consensus. Active and chronic renal lesions are expressions of severe outcomes [25–28]. Other histological findings as fibrinoid necrosis, global glomerulosclerosis, arteriolosclerosis and thrombotic microangiopathy lesions will be evaluated.

(ii) Serum creatinine will be measured using enzymatic methods, calibrated to the National Institute of Standards and Technology's Liquid Chromatography with Isotope-Dilution Mass Spectrometry method. GFR creatinine will be estimated by the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) formula [29, 30]. Patients categorized in CKD stages 1–3 will be included in the clinical study. The slope of eGFR (acute, chronic and total) will be evaluated [31].

(iii) Proteinuria. Patients will collect 24-h urine for proteinuria and creatininuria (uPCR). Values of ≥0.5 g/day will be considered abnormal as reported in the CKD KDIGO guidelines [18]. We will measure the time-average proteinuria (TA-P) [32] and the slope of proteinuria [33].

Table 2. CLIgAN study: outcomes

Primary endpoint
- Between-arms difference in proteinuria reduction within 6 months in ACIgAN and within 12 months in CHRONIgAN study.
Secondary endpoints
- eGFR slope calculated as mean of individual slope obtained from individual linear regression of eGFR overtime (3 years).
- eGFR decline >40% from the baseline value.
- Composite endpoint: eGFR decline >40%, ESKD (defined as long-term eGFR ≤15 mL/min/1.73 m^2 for more than 3 months or need for maintenance dialysis or kidney transplantation) or death due to kidney disease.
- Absolute difference between last eGFR value and baseline eGFR.
- Stable renal function defined as a decline in eGFR ≤5 mL/min/1.73 m^2 at the end of 3 year follow-up.
- Mean annual change in the slope of the reciprocal of the serum creatinine concentration.
- TA-P calculated as the weighted mean of all post-randomization measurements, with weights representing the time elapsed since the previous measurement.
- Proteinuria slope calculated as mean of individual slope obtained from individual linear regression of daily proteinuria overtime (3 years).
- Complete remission of proteinuria defined as achievement of a urinary protein level <0.2 g/24 h.
- Partial remission of proteinuria defined as urinary protein level >50% or greater compared with the baseline value.

Serum creatinine, proteinuria, age and hypertension have a lower weight when histological lesions are not considered [16]. This finding highlights the importance of kidney biopsy not only for diagnosis, but also for personalized treatment.

Outcome measures

Table 2 shows the primary and secondary endpoints that will be evaluated in the two RCTs. The primary endpoint of the proteinuria reduction between two arms will be assessed at 6 months in the ACIgAN trial and at 12 months in the CHRONIgAN study. This surrogate endpoint for kidney disease progression in clinical trials has been recently suggested by Levey *et al.* [34] and Inker *et al.* [35]. The secondary outcomes are as follows: (i) the surrogate endpoint eGFR slope calculated as the mean of individual slope obtained from individual linear regression of eGFR overtime (3 years); (ii) sustained percentage decline in eGFR >40% overtime (at least 4 weeks); and (iii) the crude endpoint initiation of maintenance dialysis for at least 4 weeks, kidney transplantation and death for kidney failure as suggested by the International Consensus definition of clinical trial outcomes for kidney failure [36]. The secondary endpoints will be evaluated every 6 months and analysed over a 3-year follow-up period.

Sample size calculation

ACIgAN. Data from the literature [20, 21, 37, 38] show a difference in renal survival between corticosteroids and controls when the researchers assumed a difference of 50% in the primary endpoint (i.e. in the between-arms difference of delta 24-h proteinuria from baseline to 6 months) as clinically relevant. Therefore, we assume that a mean delta proteinuria (±SD) from baseline to 6 months in patients treated with RASB alone (control arm) is 0.6 ± 1.0 g/24 h versus a mean delta proteinuria (±SD) from baseline to 6 months in patients treated with RASBs and corticosteroids (experimental arm), that is 1.2 ± 1.0 g/24 h. Based on these assumptions, we calculated a sample size of 132 patients (66 patients per group including a 10% dropout rate) for a power of 90%, a two-sided significance level of 0.05 and 3 years of recruitment. If the number of enrolled patients is insufficient, the recruitment period will be extended for 2 years.

CHRONIgAN. Data from the literature [11–13] suggest a difference of renal survival between SGLT2is and controls. Here the researchers assumed a difference of 40% in the primary endpoint (i.e. in the between-arms difference of delta 24-h proteinuria from baseline to 12 months) as clinically relevant. Therefore, we assume that a mean delta proteinuria (±SD) from baseline to 12 months in patients with RASBs alone is 0.6 ± 1.0 g/24 h versus a mean delta proteinuria (±SD) from baseline to 12 months in patients treated with dapagliflozin and RASB that is 1.0 ± 1.0 g/24 h. Based on these assumptions, we have calculated a sample size of 294 patients (147 patients per group including a 10% dropout rate) for a power of 90%, a two-sided significance level of 0.05 and 3 years of recruitment. If the time-recruitment is insufficient, the recruitment period will be extended for 2 years.

Ethical aspects

The local ethics committees will approve the protocol. It will be carried out according to the declaration of Helsinki (IV adaption). Every patient will be informed about goals, expected benefits and possible risks, and rights to refuse or to withdraw at any time.

Statistical analysis

Quantitative variables will be summarized in the presence of normal distribution values as mean ± SD or median and interquartile ranges in the presence of non-normally distributed variables. The between-arms comparisons of continuous variables will be performed by independent *t*-test or Mann–Whitney *U* test, as appropriate. The between-arms difference of the primary endpoint (i.e. in the between-arms difference of delta 24-h proteinuria from baseline to 6 months in the ACIgAN trial and to 12 months in the CHRONIgAN trial) will be expressed as mean difference and 95% CI. Categorical variables will be presented as absolute and percentage frequency. Proportions will be compared using the Pearson's X^2 test or Fisher's test, as appropriate. The time-to-event analysis will be performed by the Kaplan–Meier curves by comparing the experimental and control group by the log-rank test. Multivariate analysis will be based on Cox's regression proportional hazard method and used to assess the relative risk associated with possible baseline prognostic factors such as sex, age, serum creatinine, eGFR, hypertension, histological lesions and therapy.

Primary endpoint assessment will be done measuring the difference of proteinuria at baseline and at 6 months in ACIgAN study and 12 months in CHRONIgAN study. As the first approach, the intention-to-treat analysis will be conducted in all randomized patients, irrespective of adherence to the assigned treatment. A per-protocol analysis will be also performed. A secondary analysis by linear mixed models (LMM) or generalized estimating equations (GEE) will also be performed to take into account the effect switching on the study outcomes and endpoints between arms, after 6 months for the ACIgAN trial and 12 months for the CHRONIgAN trial. The choice between the two analyses (LMM versus GEE) will closely depend on the distribution/type of the outcome variables in our study cohorts. In these models, data will be expressed as regression coefficients, 95% CIs and P-value.

All analyses will be performed using SPSS for Windows, 17.0 (SPSS Inc., North Sydney, Australia) and STATA/IC 13.1 for Windows (College Station, TX, USA). A P-value <0.05 will be considered statistically significant.

DISCUSSION

Systematic reviews and meta-analyses [9, 10, 37, 38] conducted on adult IgAN patients have demonstrated that corticosteroids have beneficial effects on the outcome of the disease. A recent meta-analysis [38] on the efficacy and safety of the immunosuppressive therapies in IgAN patients demonstrated that corticosteroids slow the progression of renal damage with minimal AEs. Therefore, Tan *et al.* [37] recommended corticosteroids as the first line of immunosuppressive therapy. However, the Supportive versus Immunosuppressive Therapy for the treatment of Progressive IgA Nephropathy (STOP-IgAN) study [20] and the Therapeutic Evaluation of Steroids in IgA Nephropathy Global Study (TESTING) clinical trial [21] showed a high percentage of side effects caused by long-term therapy with corticosteroids and immunosuppressive agents. To avoid side effects, we have decided to administer pulse and oral corticosteroids for a short time (3 months) to care for the active renal lesions.

None of these trials first considered the type of renal lesions observed in the kidney biopsy as the basis for the choice of therapy. This bias resulted in the administration of corticosteroids in patients with chronic renal lesions who did not need this therapy. Moreover, those patients were enrolled in RCTs after a long run-in phase (3–6 months). During that time, the active renal lesions became irreversible and chronic; thus, they did not benefit from corticosteroids. Finally, the recent systematic review and meta-analysis of the Cochrane Library [38] concluded that corticosteroids have undetermined adverse effects due to the scarcity of the studies.

RASBs have been used in many RCTs for the treatment of CKD [39, 40] and it has been demonstrated that these drugs delay the decline of kidney function in patients with IgAN. Thus, the KDIGO guidelines suggest the use of RASBs in the treatment of IgAN [5] because they stabilize systemic and renal blood pressure, and reduce the traffic of proteins and the decline of eGFR. However, RASBs could not be sufficient to reduce proteinuria. Therefore, we have decided to switch the non-responder patients of the control arms to RASBs in combination with corticosteroids after 3 months in ACIgAN trial and to RASBs in combination with SGLT2i after 12 months in CHRONIgAN study.

SGLT2is have the favourable effect of slowing the decline of renal function in patients with diabetic nephropathy type 2, as shown in three RCTs in which different SGLT2is such as canagliflozin [12], empagliflozin [11] and dapagliflozin [13] were administered. Recently, Wheeler *et al.* [14] demonstrated that dapagliflozin reduced the CKD risk in IgAN patients. However, the Dapagliflozin in Chronic Kidney Disease (DAPA-CKD) study was not specifically designed for this disease and a low percentage of patients did not receive kidney biopsy.

SGLT2is reduce the decline of renal function inhibiting the glucose/sodium reabsorption at the proximal tubule level and modulate the hyperfiltration via tubule-glomerular feedback [41]. A systematic review and meta-analysis of pooled data from four cardiovascular studies revealed that SGLT2is reduced the risk of composite renal outcomes regardless of the baseline levels of renal function and baseline RASBs used [42]. The available evidence indicates that the renal effects may be a class effect of SGLT2i.

Finally, the CLIgAN study includes an ancillary biomolecular study to uncover biomarkers in responders and non-responders to the designed therapy protocols and to determine associations between molecular pathways and clinical endpoints.

In conclusion, we have designed an independent clinical study to evaluate the effect of corticosteroids combined with RASBs in biopsy-proven IgAN patients with active renal lesions and the effect of dapagliflozin combined with RASBs in patients with chronic renal lesions at high or very high CKD risk. The patients of the control arms will receive RASBs according to the KDIGO guidelines [5]. The kidney biopsy will be the principal keynote not only for the enrolment of patients, but also for personalized therapy.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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AUTHORS' CONTRIBUTIONS

All the authors contributed to design of the study and to write the manuscript. All the authors revised and approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

F.P.S. is a member of the *CKJ* editorial board. The other authors declared no competing interests.

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