1 SUMMARY

Full title	Treatment of IGa nEphropathy according to Renal lesions
Acronym	TIGER
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Scientific Director	*Dr K El Karoui – Renal Transplantation and Nephrology Department - Henri Mondor Hospital - 51 Av du maréchal de Lattre de Tassigny 94010 Créteil*
Sponsor	Assistance Publique – Hôpitaux de Paris
Scientific justification	Currently, IgAN treatment recommendations are only based on clinico-biological parameters. Steroids therapy appears to have a major role in IgAN treatment, but previous studies evaluating steroids lacked of optimal control group and reproducible evaluation criteria. No prospective study (including ongoing studies) with optimal RAS blockade had included renal pathology in patients selection criteria, although histological evaluation improves patients prognosis prediction. Until now, the lack of a reliable histological classification has precluded the use of histological lesions to evaluate IgAN prognosis and treatment. Given the recently identified major prognostic role of histological lesions in IgAN, we propose to introduce renal pathology to guide the treatment of IgAN in a multicenter study, using currently validated evaluation criteria of chronic kidney disease progression.
Primary objective and assessment criterion	**Primary objective** To evaluate the efficacy of early corticotherapy + RAS blockade (versus RAS blockade alone) after 2 years of evolution in IgAN patients with severe histological lesions **Assessment criterion** <u>Failure at 24 months, defined as:</u> - proteinuria/creatininuria ratio (PCR) > 0,5 g/g or mGFR < 80% of initial mGFR (or eGFR if unavailable) - or loss of more than 10 ml/min/1,73m^2 of initial mGFR (or eGFR if unavailable) - or end stage renal disease (ESRD) - or renal transplantation - or death
Secondary objectives and assessment criteria	**Secondary objectives** - to evaluate the efficacy of early corticotherapy + RAS blockade (versus RAS blockade alone) at 6 and 12 months of evolution - to compare the evolution of histological lesions between treatment groups at 12 months - to compare the evolution of measured GFR (mGFR) between treatment groups at 12 and 24 months (or estimated GFR (eGFR) if unavailable) - to compare the evolution of proteinuria in each group - to compare the quality of life in each therapeutic group - to assess the tolerance of treatments of each therapeutic group - to identify prognosis markers of failure at 24 months **Assessment criteria** <u>Failure at 6 months will be defined as:</u> - PCR > 0.75 g/g

	- or PCR > 0.5 g/g and >30% of initial PCR - or eGFR < 80% of initial eGFR - or ESRD - or renal transplantation - or death. <u>Failure at 12 months will be defined as:</u> - PCR > 0.75 g/g - or PCR > 0.5 g/g and > 30% of initial PCR - or mGFR < 80% of initial mGFR (or eGFR if unavailable) - or ESRD - or renal transplantation - or death. <u>Histological lesions evolution at 12 months :</u> The evolution of histological lesions will be assessed as the proportion of patients of both therapeutic group with persistent severe histological lesions in repeat kidney biopsy at 12 months. <u>Measured GFR (mGFR or eGFR if unavailable) evolution:</u> The evolution of GFR at 12 and 24 months will be assessed as: - the absolute value of GFR - the absolute difference of GFR from the baseline - the annual degradation (ml/min /1,73m^2/year) of GFR during the 24 months <u>Proteinuria evolution</u> The evolution of proteinuria will be assessed as : - the absolute value of proteinuria at 12 and 24 months - the absolute difference of proteinuria from baseline at 12 and 24 months <u>Identification of prognosis markers of failure at 24 months:</u> Clinical, histological, and biological data (including PCR ratio, eGFR and mGFR, renal histological lesions) will be compared between patients with or without failure. <u>Comparison of side effects in each therapeutic group.</u> <u>Comparison of life quality scale in each therapeutic groupwith SF36 scale at 12 and 24 months</u>
Experimental design	Multicenter, open-labelled randomized phase III trial
Population involved	≥18 years IgA Nephropathy patients
Inclusion criteria	a. Age ≥18 years b. IgAN diagnosed on renal biopsy < 45 days c. PCR ratio >0.75 g/g (within 30 days before or after the renal biopsy) d. Renal biopsy with at least 8 glomeruli, disclosing at least 2 criteria among: • mesangial proliferation (according to Oxford criteria) • endocapillary proliferation (according to Oxford criteria) • tubulointerstitial fibrosis (according to Oxford criteria) >25% of the biopsy • segmental glomerulosclerosis (according to Oxford criteria)

	• ≥10% cellular/fibrocellular crescents. e. Patient with Social Security System Insurance or CMU f. Patient having signed an informed consent
Non-inclusion criteria	a. >30% increase of serum creatinine within 15 days after starting RAS blockade therapy b. >50% cellular/fibrocellular crescents or >50% tubulointerstitial fibrosis or >50% globally sclerotic glomeruli c. >50% plasma creatinine increase within the last 3 months before the renal biopsy d. Nephrotic syndrome with minimal change disease and IgA deposits e. eGFR <20 ml/min/1,73m^2 (CKD-EPI formula) within 30 days before or after the renal biopsy f. Uncontrolled blood pressure (Systolic blood pressure >180 mmHg or diastolic blood pressure > 110 mmHg) g. Previous corticosteroids treatment (>20 mg/d during more than 15 days, within the last 3 months before the renal biopsy) h. Pregnancy or breast feeding or women without sufficient contraception i. Secondary known forms of IgAN j. Henoch-Schoenlein purpura k. Additional other chronic renal disease l. Contraindication for immunosuppressive therapy, including active intestinal bleeding, active gastric or duodenal ulcer; active infection; any malignancy in a last years before the inclusion; severe psychiatric disease; living vaccines; anti-inflammatory dosages of acetylsalicylic acid m. Contraindication for RAS blockade therapy n. Known allergy or intolerance to corticoids or lactose o. Organ transplant patient **The absence of measured GFR availability on the site is not an exclusion criterion.**
Treatment being tested	3 IV pulses steroids followed by oral steroids for 4 months
Benchmark treatment	Renin angiotensin system blockade
Risks added by the research	*B*
Number of subjects chosen	122
Number of centres	27
Research period	Inclusion period : 24 months Participation period : 24 months+ 21 days max Total research period : 48 months
Number of inclusions expected per centre and per month	0.3
Funding source	French Health Ministery
Data Safety Monitoring Board anticipated	Non