

Project title:

EUROPEAN VALIDATION STUDY OF THE OXFORD CLASSIFICATION OF IGA NEPHROPATHY (VALIGA)

Length of the Project:

From June 1, 2010 to December 1, 2012

Principal Investigator:

Rosanna Coppo

Proposed research:

IgA nephropathy (IgAN), the most common glomerular disease worldwide, is potentially progressive to renal failure. In individual patients its course is unpredictable before development of severe proteinuria, hypertension, reduced glomerular filtration rate and renal fibrosis. There is a need to detect progressive cases in early stages, when a therapeutic intervention is more likely to be effective.

A breakthrough report just published from an International Consensus - based on a retrospective analysis of 265 adults and children with IgAN from four continents - focuses on prognostic information provided by renal biopsy. According to this Oxford Classification of IgAN, four pathological features (mesangial hypercellularity, segmental glomerulosclerosis, endocapillary hypercellularity, and tubular atrophy/interstitial fibrosis) predict renal outcome independently from all clinical indicators at the time of biopsy and during follow up (Kidney International 2009;76:534-45; and Kidney International 2009;76:546-56). The limited number of patients and their heterogeneous origin indicate a need for validation studies involving large cohorts of patients. The proposed study will investigate European patients and the results will be complementary to those from similar studies in North America and Asia, allowing a global perspective on the value of these predictive factors. Biopsy-proven IgAN with long follow-up or rapidly progressive course (about 500 cases) will be enrolled by 26 Centers of Nephrology and Renal Pathology from 9 Countries. Renal biopsies will be scored by the local pathologist and centrally reviewed in Oxford. Clinical data at renal biopsy and during the follow-up will be provided by local Nephrologists to the Coordinating Center. Statistical analysis will be performed by Canadian experts.

This multicenter, multinational study supported by the ERA-EDTA Working Group of Immunonephrology will provide information beyond the validation of the Oxford classification of IgAN, aiming at detecting for each lesion the most effective treatment and the "point of no return" when no treatment is effective.

Aim of the research:

1) The relevance for Europe is because IgAN is a common cause of CKD, progressing to need of renal replacement treatment. It is the most dominant glomerular disease in Europe, accounting for 20-30% of renal biopsies and representing half of all cases of glomerulonephritis. The 20-year cumulative renal surviving rate ranges from 14 to 39%. Its progression to end-stage renal disease occurs over a wide time range from a few months to more than 50 years. Hence, IgAN is likely to be underdiagnosed particularly in elderly patients with hypertension found to have CKD of unknown origin. The ERA-EDTA registry reported in 1991 that 67% of patients with IgAN enter a chronic dialysis program as young adults (24-54 year-old). Knowing the slow function decline in IgAN, it is likely that many of these progressive cases began in childhood. Thus a broad spectrum of patients are affected by this disease and therefore the study has a potential of benefit in all age groups by its focus on detecting new risk factors for progression.

2) The study proposed will place European nephrologists and renal pathologists in a worldwide network of scientist, complementing/augmenting similar validation studies ongoing in other continents, including North America and Asia. This proposal will also provide updated information for European patients.

3) This study will provide a template for collaboration among European nephrologists and renal pathologists in methodology related to scoring renal biopsies, collecting clinical data and participating in data analysis (in collaboration with experts from Canada familiar with the methodology used in the original Oxford classification).

4) This study, proposed by the newly formed ERA-EDTA Working Group of Immunonephrology, will provide added value by establishing a European infrastructure network of nephrologists and pathologists which can act as a nidus for future Europe-wide investigations on glomerular and immunological renal disorders.

List of the papers published in peer review journals:

- 1) Coppo R, Troyanov S, Bellur S, Cattran D, Cook HT, Feehally J, Roberts IS, Morando L, Camilla R, Tesar V, Lunberg S, Gesualdo L, Emma F, Rollino C, Amore A, Praga M, Feriozzi S, Segoloni G, Pani A, Cancarini G, Durlik M, Moggia E, Mazzucco G, Giannakakis C, Honsova E, Sundelin BB, Di Palma AM, Ferrario F, Gutierrez E, Asunis AM, Barratt J, Tardanico R, Perkowska-Ptasinska A; VALIGA study of the ERA-EDTA Immunonephrology Working Group. Validation of the Oxford classification of IgA nephropathy in cohorts with different presentations and treatments. *Kidney Int.* 2014 Oct; 86(4):828-36. D.O.I.: 10.1038/ki.2014.63. Epub 2014 Apr 2. PubMed PMID: 24694989; PubMed Central PMCID: PMC4184028.
- 2) Tesar V, Troyanov S, Bellur S, Verhave JC, Cook HT, Feehally J, Roberts IS, Cattran D, Coppo R; VALIGA study of the ERA-EDTA Immunonephrology Working Group. Corticosteroids in IgA Nephropathy: A Retrospective Analysis from the VALIGA Study. *J Am Soc Nephrol.* 2015 Sep; 26(9):2248-58. doi: 10.1681/ASN.2014070697. Epub 2015 Feb 12. PubMed PMID: 25677392; PubMed Central PMCID: PMC4552116.
- 3) Feehally J, Coppo R, Troyanov S, Bellur SS, Cattran D, Cook T, Roberts IS, Verhave JC, Camilla R, Vergano L, Egido J, Wiecek A, Karkoszka H, Tesar V, Maixnerova D, Ots-Rosenberg M, Quaglia M, Rollino C, Magistroni R, Cusinato S, Cravero R, Peruzzi L, Lundberg S, Gesualdo L, Cancarini G, Feriozzi S, Ferrario F; VALIGA study of ERA-EDTA Immunonephrology Working Group. Tonsillectomy in a European Cohort of 1,147 Patients with IgA Nephropathy. *Nephron.* 2016;132(1):15-24. doi: 10.1159/000441852. Epub 2015 Nov 20. PubMed PMID: 26586175.
- 4) Barbour SJ, Espino-Hernandez G, Reich HN, Coppo R, Roberts IS, Feehally J, Herzenberg AM, Cattran DC; Oxford Derivation, North American Validation and VALIGA Consortia; Oxford Derivation North American Validation and VALIGA Consortia. The MEST score provides earlier risk prediction in IgA nephropathy. *Kidney Int.* 2016 Jan;89(1):167-75. doi: 10.1038/ki.2015.322. PubMed PMID: 26759049.
- 5) Coppo R, Lofaro DD, Camilla RR, Bellur S, Cattran D, Cook HT, Roberts IS, Peruzzi L, Amore A, Emma F, Fuiano L, Berg U, Topaloglu R, Bilginer Y, Gesualdo L, Polci R, Mizerska-Wasiak M, Caliskan Y, Lundberg S, Cancarini G, Geddes C, Wetzels J, Wiecek A, Durlik M, Cusinato S, Rollino C, Maggio M, Praga M, K Smerud H, Tesar V, Maixnerova D, Barratt J, Papalia T, Bonofiglio R, Mazzucco G, Giannakakis C, Soderberg M, Orhan D, Di Palma AM, Maldyk J, Ozluk Y, Sudelin B, Tardanico R, Kipgen D, Steenbergen E, Karkoszka H, Perkowska-Ptasinska A, Ferrario F, Gutierrez E, Honsova E. Risk factors for progression in children and young adults with IgA nephropathy: an analysis of 261 cases from the VALIGA European cohort. *Pediatr Nephrol.* 2016 Aug 25. [Epub ahead of print] PubMed PMID: 27557557.

List of the presentations done at major congresses/meetings:

Abstracts

1) 2012

Congress of the American Society of Nephrology, Renal Week 2012, San Diego, CA, USA, 30/12/2012-4/11/2012

Oral communication:

"VALIGA: Preliminary Clinical Results from the European Collaborative Database of 1178 IgA Patients Designed to Validate the Oxford Classification". Coppo R, Troyanov D, Cattran DC, Feehally J, Cook TH, Roberts I, Morando L, Bellur S, Camilla R, Immunonephrology Working Group, ERA-EDTA.

2) 2013

A) IgA nephropathy Symposium, Nanjing meeting satellite to WCN, June 2013 and B) IPNA Congress Shanghai, August –September 2013, both oral presentations by Rosanna Coppo

"Risk factors for progredition in children with IgA nephropathy: data from a European cohort. Roberta Camilla, Rosanna Coppo, Shubha Bellur, Daniel Cattran, Terence Cook, John Feehally, Stéphan Troyanov, Francesco Emma, Costantinos Giannakakis, Alessandro Amore, Gianna Mazzucco, Ulla Berg, Magnus Soderberg and Malgorzata Mizerska-Wasiak on behalf of VALIGA study group

3) 2013

50th ERA-EDTA Congress, Istanbul, Turkey, 18-21/05/2013

Oral communication:

"Risk factors for progression in children with IgA nephropathy: data from a European cohort". Camilla R, Coppo R, Bellur S, Cattran D, Cook T, Feehally J, Troyanov S, Emma F, Giannakakis C, Amore A, Mazzucco G, Berg U, Soderberg M, Mizerska-Wasiak M. on behalf of VALIGA study group

4) 2013

50th ERA-EDTA Congress, Istanbul, Turkey, 18-21/05/2013

Poster: "Tonsillectomy in a pan-European cohort of 1147 patients with IgA nephropathy". Camilla R, Coppo R, Bellur S, Cattran D, Cook T, Feehally J, Troyanov S, Roberts I, Vergano L, Morando L. on behalf of VALIGA study group

5) 2014

51th ERA-EDTA Congress, Amsterdam 2014

Minilecture. "VALIGA: a pan European collaborative study on IgA nephropathy"

Rosanna Coppo

6) 2015

World Congress of Nephrology (WCN), Cape Town March 13-17 2015: Symposium on IgA nephropathy: lecture by Rosanna Coppo

"The Oxford classification of IgAN: insights from the VALIGA study"

7) 2016

ISN Nexus Symposium 2016: Translational Immunology in Kidney Diseases. April 14-17 Berlin. ERA-EDTA-INS Join Symposium: Lecture by Rosanna Coppo

"Corticosteroids in IgA nephropathy: lessons from recent studies"

8) 2016

53 Congress of the ERA-EDTA Vienna, 21-24 May, 2016, Oral communication

PROGRESSIVE IgA NEPHROPATHY AND DEFECTIVE COMPLEMENT INHIBITOR CD46 MRNA EXPRESSION IN PERIPHERAL MONONUCLEAR CELLS Rosanna Coppo, Licia Peruzzi, Elisa Loiacono, Massimiliano Bergallo, Maria Luisa Russo, Alessandro Amore, Sigrid Lundberg, Dita Maixnerova, Vladimir Tesar, Agnieszka Perkowska-Ptasinska,

Magdalena Durlak, Dimitris Goumenos, Miltiadis Gerolymos, Kresimir Galesic, Luka Toric, Aikaterini Papagianni, Maria Stangou, Malgorzata Mizerska-Wasiak, Maria Roszkowska-Blaim, Loreto Gesualdo, Eustacchio Montemurno, Luisa Benozzi, Stefano Cusinato, Tomasz Hryszko, Marian Klinger, Dorota Kamińska, Magdalena Krajewska, Alexandra Krutova; POST-VALIGA study of the Immunonephrology Working Group of the ERA-EDTA.

9) 2016

57 National Congress of the Italian Society of Nephrology October 12-15, 2016. Lecture presented by Rosanna Coppo

"From VALIGA to STOP-IgAN and new treatments."

10) 2016

IgAN Royal Society of Medicine, London November 9, 2016. Outcomes from the VALIGA Study Group in Lecture presented by Rosanna Coppo

11) 2017

54 Congress of the ERA-EDTA, Madrid June 2-6, 2017, Poster SP 104

IS THERE LONG-TERM VALUE OF PATHOLOGY SCORING IN IgA NEPHROPATHY? A VALIGA UPDATE

Rosanna Coppo, G D'Arrigo, G Tripepi, ML Russo, I.S.D Roberts, S Bellur, D Cattran, TH Cook, J Feehally, V Tesar, D Maixnerova, S Lundberg, AM Di Palma, F Emma, C Rollino, M Praga, L Biancone, A Pani, J Barratt, L Del Vecchio, F Locatelli, A Pierucci, Y Caliskan, A Perkowska-Ptasinska, Ballarin JC.

12) 2017

54 Congress of the ERA-EDTA, Madrid June 2-6, 2017 Lecture presented by Rosanna Coppo.

"IgA nephropathy: the landscape after the VALIGA study"