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

Estimated length / Total length (if the project was already concluded): 30 months
Application presented at the First ERA-EDTA research Call, July 1st 2009.
Starting date: 01/06/2010
Ending Date: 01/12/2012
Project successfully ended.

Name of the Principal Investigator:
Rosanna Coppo

List of the collaborators and List of the centres / institutions involved:
VALIGA centers lists
NEPHROLOGISTS
Tesar V, Maixnerova D (Prague, Czech Republic), Lundberg S (Stockholm, Sweden), Gesualdo L (Foggia-Bari, Italy), Emma F, Fuiano L (Rome, Italy), Beltrame G, Rollino C (Turin,Italy), Coppo R, Amore A, Camilla R, Peruzzi L (Turin,Italy), Praga M (Madrid, Spain), Feriozzi S, Polci R (Viterbo, Italy), Segoloni G, Colla L (Turin, Italy), Pani A, Angioi A, Piras D (Cagliari, Italy), Feehally J (Leicester, United Kingdom), Cancarini G, Ravera S (Brescia, Italy), Durlik M(Warsaw, Poland), Moggia E (Cuneo, Italy), Ballarin J (Barcelona, Spain), Di Giulio S (Rome, Italy), Pugliese F (Rome, Italy),Caliskan Y (Istanbul, Turkey), Locatelli F, DelVecchio L (Lecco, Italy), Wetzels JFM, Peters H (Nijmigen,The Netherlands), Berg U (Huddinge, Sweden), Carvalho F(Lisbon, Portugal), Maggio M (Lodi, Italy), Wiecek A(Katowice, Poland), Ots-Rosenberg M (Tartu, Estonia),Magistroni R (Modena, Italy), Topaloglu R, Bilginer Y(Ankara, Turkey), D'Amico M (Como, Italy), Stangou M(Thessaloniki, Greece), Giacchino F (Ivrea, Italy), GoumenosD, Kalliakmani P, Gerolymos M (Patras, Greece), Galesic K(Zagreb, Croatia), Geddes C (Glasgow, United Kingdom),Siamopoulos K,Balafa O (Ioannina, Greece), Galliani M,(Rome, Italy), Stratta P, Quaglia M (Novara, Italy), Bergia R, Cravero R (Biella,Italy), Salvadori M, Cirami L (Florence,Italy), Fellstrom B, Kloster Smerud H (Uppsala, Sweden),Ferrario F,Stellato T (Monza, Italy), Egido J, Martin C(Madrid, Spain), Floege J, Eitner F (Aachen, Germany), LupoA, Bernich P(Verona, Italy), Mene` P (Rome, Italy), Morosetti M (Ostia, Italy), van Kooten C, Rabelink T, Reinders MEJ(Leiden, The Netherlands), Boria Grinyo JM (Barcelona,Spain), Cusinato S, Benozzi L (Borgomanero, Italy), SavoldiS, Licata.C(Cirie, Italy), Mizerska Wasiak M (Warsaw,Poland), Martina G, Messuerotti A (Chivasso, Italy), DalCanton A,Esposito C, Migotto C (Pavia, Italy), Triolo G,Mariano F (Turin, Italy), Pozzi C (Cinisello B., Italy), BoeroR (Turin, Italy).

PATHOLOGISTS
Mazzucco G (Turin, Italy), Giannakakis C (Rome, Italy),Honsova E (Prague, Czech Republic), Sundelin B(Stockholm, Sweden), Di Palma AM (Foggia-Bari, Italy),Ferrario F (Monza, Italy), Gutie´rrez E (Madrid, Spain),Asunis AM (Cagliari, Italy), Barratt J (Leicester, UK),Tardanico R (Brescia, Italy), Perkowska-Ptasinska A (Warsaw,Poland), Arce Terroba J(Barcelona, Spain), Fortunato M(Cuneo, Italy), Ozluk Y, Kilicaslan I (Istanbul, Turkey),Steenberger E (Nijmigen, The Netherlands), Soderberg M(Huddinge, Sweden), da Costa Ferreira AC (Lisbon, Portugal),Riispere Z (Tartu, Estonia),

FFurci L (Modena, Italy),Orhan D (Ankara, Turkey), Kipgen D (Glasgow, UK),Casartelli D (Lecco, Italy), Galesic Ljubanovic D (Zagreb,Croatia),Bertoni E (Florence, Italy), Cannata Ortiz P (Madrid, Spain), Groene HJ (Heidelberg, Germany),Stoppacciaro A (Rome, Italy), Bajema I, Bruijn J (Leiden, TheNetherlands), Fulladosa Oliveras X (Barcelona, Spain),Maldyk J (Warsaw, Poland), Ioachim E (Ioannina, Greece).

Proposed research:

(Summary presented in the application)

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.

Progress and results at the Study conclusion:

VALIGA, a pan European research project enrolling 1147 patients with IgA nephropathy

The research has represented a milestone in the European collaboration for investigating risk factors for progression of IgA nephropathy, the most common primary glomerular disease in the world.

The initial assessment, as approved by the ERA-EDTA SAB, included **26** Centres of Nephrology and Renal Pathology, from **9** European Countries which had agreed, in June 2009 at the first submission, on providing clinical data and renal biopsy material for the reviewing process according to the Oxford Classification for IgA Nephropathy. A total of **500** cases were forecasted. This was a project proposed by the Immunonephrology WG (IWG), therefore it was publicized in the IWG website. Since then several other centres asked to participate in this study and they were all accepted, because it was actually the original aim of the IWG. At end of enrolment, in January, 2012, the VALIGA Study included **55 Centres from 13 different countries** with a total of **1252** cases enrolled. 2504 clinical spreadsheets and 1252 pathology scoresheets were received and checked in the Coordinating Center in Turin, Italy. Meanwhile, 1252 renal biopsy slides were sent to Oxford for review. After exclusion of cases with insufficient renal biopsy a material for review, **1147** cases were analysed.

The first results analysed are reported in the publication Kidney International doi:10.1038/ki.2014.63, the Abstract is reported below:

The Oxford Classification of IgA Nephropathy (IgAN) identified mesangial hypercellularity (M), endocapillary proliferation (E), segmental glomerulosclerosis (S), and tubular atrophy/interstitial fibrosis (T) as independent predictors of outcome. Whether it applies to individuals excluded from the original study and how therapy influences the predictive value of pathology remain uncertain. The VALIGA study examined 1147 patients from 13 European countries that encompassed the whole spectrum of IgAN. Over a median follow-up of 4.7 years, 86% received renin–angiotensin system blockade and 42% glucocorticoid/ immunosuppressive drugs. M, S, and T lesions independently predicted the loss of estimated glomerular filtration rate (eGFR) and a lower renal survival. Their value was also assessed in patients not represented in the Oxford cohort. In individuals with eGFR less than 30ml/min per 1.73m2, the M and T lesions independently predicted a poor survival. In those with proteinuria under 0.5 g/day, both M and E lesions were associated with a rise in proteinuria to1 or 2 g/day or more. The addition of M, S, and T lesions to clinical variables significantly enhanced the ability to predict progression only in those who did not receive immunosuppression (net reclassification index 11.5%).

The VALIGA study provides a validation of the Oxford classification in a large European cohort of IgAN patients across the whole spectrum of the disease. The independent predictive value of pathology MEST score is reduced by glucocorticoid/immunosuppressive therapy.

In conclusion,

The ERA-EDTA supported VALIGA study is a successful multi center pan-European collaborative study which has obtained some relevant goals:

1) The Oxford Classification for IgA nephropathy is valid for European patients, as confirmed over 1147 cases from 13 European Countries.

2) Other sub-analyses of the rich database will allow further insights into subgroups of patients with IgA Nephropathy focusing on children or specific features as well as into the effect of treatments.

3) Last but not least, VALIGA has established an active network of Nephrologists interested in glomerular diseases, pathology and risk factors for renal disease progression. Its results are expected with great interest by the scientific community.

1) New post-VALIGA studies.

VALIGA follow-up. Updated records were obtained for study of the prolonged VALIGA follow up in 780 of the 1147 patients from 45/55 Centers of the original VALIGA study. The median follow-up time was extended from 4.7 (interquartile range 2.4-7.9) years in the original VALIGA to 7.1 (4.1-10.8) years. At 15 years of follow-up after renal biopsy there were still 98 patients at risk. Data were presented at the ERA-EDTA Congress in 2016 as a poster "IS THERE LONG-TERM VALUE OF PATHOLOGY SCORING IN IgA NEPHROPATHY?" and the manuscript is in preparation.

2) POST-VALIGA studies:

The establishment of the VALIGA network supported by the Immunonephrology Working Group has allowed relevant new initiatives, based on new samples collection from patients belonging to the VALIGA study group. The patients enrolled in the original VALIGA were very well characterized from clinical and renal pathology features, and were investigated after a follow up of several years with precise detection of rate of GFR decline. In these patients two studies were performed. The first one aiming at detecting correlations between cell surface complement regulatory protein mRNA expression and previous clinical course and renal function decline is under publication. Another study on the switch from proteasome to immunoproteasome in peripheral blood cells of patients is under preparation for publication.

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 lgA 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 progrogression 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 NEPHPHROPATHY AND DEFECTIVE COMPLEMENT INHIBITOR CD46 MRNA EXPRESSION IN PERIPHERAL MONUCLEAR CELLS Rosanna Coppo, Licia Peruzzi, Elisa Loiacono, Massimilano Bergallo, Maria Luisa Russo, Alessandro Amore, Sigrid Lundberg, Dita Maixerova, Vladimir Tesar, Agnieszka Perkowska-Ptasińska,

Magdalena Durlik, 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"

As of February 2018