Advances in the European Validation Study of the Oxford Classification of IgA Nephropathy (VALIGA)

One of the major aims of the IWG is to facilitate European Nephrologists interested in the area of immune-mediated diseases to establish networks and perform collaborative studies.

In June 2009 an application was presented, on behalf of the IWG, for the first ERA-EDTA Research Call, which was awarded among the first 3 projects accepted for funding (May 2010). The study started in June 2010 and was planned to last 18 months, thus ending December 2011.

The scientific project started from the publication of a breakthrough report produced by an International Consensus Group—based on a retrospective analysis of 265 adults and children with IgA nephropathy from four continents – focused on prognostic information provided by renal biopsy. According to this Oxford Classification of IgA Nephropathy, 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 Int 2009;76:534-45; Kidney Int 2009;76:546-56 and Kidney Int Kidney 2010;77:921-7).

The limited number of patients and their heterogeneous origin indicated a need for validation studies involving larger cohorts of patients. VALIGA was planned to investigate European IgA nephropathy patients also in order to gather results complementary to those from similar studies in North America and Asia, allowing a global perspective on the value of these factors to predict the clinical outcome of patients with IgA Nephropathy.

VALIGA INITIAL ASSESSMENT. The study entry criteria include biopsy-proven IgA Nephropathy with long follow-up or rapidly progressive course with renal biopsy material available for reviewing and scoring according to the new classification. Renal biopsies are to be scored by the local pathologist and centrally reviewed in Oxford. Complete clinical data at renal biopsy and during the follow-up are provided by local nephrologists to the coordinating center. Statistical analysis will be performed by the Canadian experts who participated also in the steering committee of the initial Oxford Study.

The initial assessment included 25 Centres of Nephrology and Renal Pathology, from 9 European Countries, which had agreed, in June 2009 during 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. Since this was a project proposed by the IWG it was publicized during its Symposium in Munich and published on the IWG website. Since then several other centres asked to participate in this study, and since this was actually the original aim of the IWG, they were all accepted.

PRESENT ADVANCEMENT. At July 2011 the VALIGA Study includes 52 Centers of Nephrology and Renal Pathology from 13 European Countries (Croatia, Czech Republic, Estonia, Germany, Greece, Italy, Poland, Portugal, Spain, Sweden, The Netherlands, Turkey, United Kingdom) with a total of 1227 cases enrolled. 886 cases are completed (both clinical spreadsheets and pathology scoresheet review were received) of which 742 renal biopsy slides were sent to Oxford for review.

Taking into consideration the increase in the number of centres, cases and the amount of work involved, the deadline for the termination of the VALIGA project has been postponed from December 2011 to December 2012. At this point, each Clinical and Pathology Center in Europe which sent clinical spreadsheets and pathology scoresheets have to be thanked for the work done. Laura Morando, PhD who is taking care of the clinical data-base in Turin is doing a terrific work and should be thanked. Prof Ian Roberts is going to have a very hard work in reviewing the
pathology slides which are arriving in Oxford and DR Stéphan Troyanov (Montreal) will do the hard final statistical work.

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 “point of no return” when no treatment is effective. But beside the scientific result, the enthusiastic participation of so many centers in Europe for a spontaneous study, is a valuable result for the scientific community of Nephrologists

Prof. Rosanna Coppo, Nephrology, Dialysis and Transplantation Unit, Regina Margherita Children’s University Hospital, Torino, Italy
Advances in the European Validation Study of the Oxford Classification of IgA Nephropathy (VALIGA)
Name of Applicant:
First name: Rosanna
Last name: Coppo

Endorsed by the ERA-EDTA working group of Immunonephrology

EUROPEAN VALIDATION STUDY
OF THE OXFORD CLASSIFICATION OF IGA NEPHROPATHY (VALIGA)
The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification

Consensus Classification of IgAN (265 cases)
206 adults 59 children
## Age and Geographical Origin of Study Cohort of 265 Cases of IgA Nephropathy

<table>
<thead>
<tr>
<th>Region</th>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>206</td>
<td>59</td>
</tr>
<tr>
<td><strong>Asia</strong></td>
<td>48</td>
<td>14</td>
</tr>
<tr>
<td><strong>Europe</strong></td>
<td>73</td>
<td>21</td>
</tr>
<tr>
<td><strong>North and South America</strong></td>
<td>85</td>
<td>24</td>
</tr>
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</table>
Oxford study
Enrolment criteria:
1) likely progressive IgAN (proteinuric patients)
2) follow-up > 1 year in order to allow calculation of e-GFR decline

Focus on the most common form of mildly severe IgAN in which markers of disease progression are needed

Excluded from enrolment in Oxford study
1) Non proteinuric likely non progressive IgAN
2) Rapidly progressive forms (severely crescentic)
At univariate analysis the variables are significantly correlated with the outcome (e-GFR decline and doubling of Cr or ESRF)

These features maintain their independent predictive value also when the multivariate analysis considers
- Clinical data at renal biopsy (e-GFR, MAP, UP)
- Clinical data at follow-up (UP and MAP during time)
Results from the Oxford study

- A systematic approach was developed to produce a histological scoring scheme in IgA nephropathy.

- A small number of lesions have been identified that are both reproducible and independent predictors of patient outcome.

- Recommendations were made for standardised reporting of renal biopsies in IgA nephropathy.

- The findings of this study require validation in other patient groups.
VALIDATION STUDY IS NEEDED in order to

• **Validate or modify** Oxford criteria in a pan European cohort (> 500 cases)

• Investigate the effect of **additional features** which had enrollment bias in the first study (rapidly progressive and non progressive cases)

• Investigate the **combined prognostic value** of adding clinical data to biological scores (e.g. proteinuria at renal biopsy or during follow-up).

• detect for each lesion **the most effective treatment and the “point of no return”** when no treatment is effective.
IgAN (dominant or codominant IgA)
• children and adults, regardless of treatment given
• 8 or more glomeruli
• at least 3 measurements of creatinine, proteinuria and blood pressure, the first of which should be within 3 months of the date of renal biopsy and the last at the end of the follow-up
• Patients having progressed to ESRD regardless of the duration of follow-up
  or
  Patients with a follow-up longer than 1 year.

Excluded: Henoch-Schönlein nephritis, and IgAN with relevant comorbid conditions such as diabetes or tumors.
Research Group

- Coordinating center: Coppo R, Turin, Italy

- Steering committee group: Coppo R, Feehally J, Roberts I, Cook T, Cattran D, Trojanov S (core group of the Oxford classification)

- Pathology review center: Roberts I (Oxford, UK)

- Statistical analysis center: Trojanov S, Cattran D (Montreal and Toronto, Canada)
Phase I: Patients enrolment

Clinical nephrology centers → List of patients with IgA nephropathy meeting the enrolment criteria → List sent to renal pathology centers

Renal pathology centers → Check availability of renal biopsy material for review

June 2011: Phase I completed

LIST OF ENROLLED CASES SENT TO THE COORDINATING CENTER
Clinical dataset

Done by nephrologists

- Demographics including date of birth, gender, ethnicity, date of biopsy.

- Clinical parameters collected within 3 months of date of biopsy (table 3) and during follow up (table 4) including:
  systolic and diastolic BP, weight, height, serum creatinine and 24hr urine protein or UP/UCr

- Treatment modalities.

June 2011: Phase I completed
Phase II: Clinical data collection and renal biopsy scoring

Clinical nephrology centers → Clinical data spreadsheet filled-in → SPREADSHEETS SENT TO THE COORDINATING CENTER

June 2011: Phase II on the way
Pathology scoresheet

Prepared by pathologist
PAS stained RB

according to the Oxford Classification the cut-off will be
  • mesangial hypercellularity score: 0.5 (equivalent to 50% of glomeruli showing mesangial hypercellularity);
  • segmental glomerulosclerosis, endocapillary hypercellularity and extracapillary proliferation: present or absent;
  • tubular atrophy/interstitial fibrosis: absent/mild (0-25%), moderate (26-50%), severe (>50%).
Phase II: Clinical data collection and renal biopsy scoring

SCORED BIOPSIES
SLIDES SENT TO THE PATHOLOGY REVIEW CENTER

June 2011: Phase II on the way
Phase III: Renal biopsy review

Renal biopsy slides reviewed, blinded to clinical data and local scoring

Pathology review center (Oxford)

June 2011: Phase III on the way

SCORESHEETS SENT TO THE COORDINATING CENTER
Phase IV: Data collection

Coordinating center

Insure clinical and pathologic spreadsheets and scoresheets completeness, communicating with each center as necessary

DATABASE SENT TO STATISTICAL ANALYSIS CENTER

June 2011: Phase IV on the way
Phase V: Statistical analysis and publication

- Statistical center
- Steering committee

Data analysis
Data analysis
Manuscript writing

Phase IV has to be done
• Database management: Laura Morando (Turin, Italy)

• Statistical analysis will be performed by the Statistical Analysis Centers (Montreal and Toronto, Canada).

• Data analysis will be overseen by the steering committee (core group of the Oxford classification: Coppo R, Feehally J, Roberts I, Cook T, Cattran D, Troyanov S)
Pathology data analysis

- Reproducibility for each pathology variable will be assessed using intraclass correlation coefficient (ICC) which was adopted for the work leading to Oxford classification.
- Continuous pathological variables will be categorized according to the rate of e-GRF decline (dichotomized in 2 groups by the median value) using receiver operating characteristic (ROC) curves.
Clinical data analysis

• Three clinical outcomes will be studied to address the predictive value of pathology variables:

[a] the rate of renal function decline (slope of eGFR);
[b] survival from a 50% reduction in renal function, or ESRD;
[c] proteinuria during follow up [as a surrogate outcome measure].
Statistical analysis

- Survival analysis using Cox regression will be performed to test the association between each pathological finding and a combined event (50% reduction in renal function or ESRD, to increase the rate of events and permit a valid multivariate analysis)
- Multivariate Cox regression will be performed. Interactions with age, ethnicity and immunosuppressive treatment will be investigated.
Name of Applicant:
First name: Rosanna
Last name: Coppo

On behalf of the ERA-EDTA working group of Immunonephrology

EUROPEAN VALIDATION STUDY
OF THE OXFORD CLASSIFICATION OF IGA NEPHROPATHY (VALIGA)
Validation of the Oxford classification of IgA nephropathy

Andrew M. Herzenberg1,6,7, Agnes B. Fogo2,6, Heather N. Reich1,6, Stéphan Trojanov3,6, Nuket Bavbek2, Alfonso E. Massar4, Tracy E. Hunley5, Michelle A. Hladunewich2, Bruce A. Ju2,10, A. J. B. Connon4 and Daniel C. Catran2

• North America
• 187 cases (adults and children)
• 4 centers form North America

NDT Advance Access published May 23, 2011

Nephrol Dial Transplant (2011) 0: 1–7
doi: 10.1093/ndt/gft295

Original Article

The Oxford classification as a predictor of prognosis in patients with IgA nephropathy

Seok Hui Kang1, Sun Ryoung Choi1, Hoon Suk Park1, Ja Young Lee1, In O Sun1, Hyeon Seok Hwang2, Byung Ha Chung1, Cheol Whee Park1, Chul Woo Yang1, Yong Soo Kim1, Yeong Jin Choi3 and Bum Soon Choi1

• Korea
• 273 cases
• 1 center
26 Centers of Nephrology and Renal Pathology from 9 European Countries (Spain, France, United Kingdom, Italy, Germany, Sweden, Poland, Netherlands, Turkey) have agreed on June 2009 upon providing clinical data and renal biopsy material available for the reviewing process according to the Oxford Classification for IgAN.

A total of 500 cases was forecasted.
52 Centers of Nephrology and Renal Pathology from 13 European Countries (Croatia, Czech Republic, Estonia, Germany, Greece, Italy, Poland, Portugal, Spain, Sweden, The Netherlands, Turkey, United Kingdom) have enrolled their patients.
Update July 2011:

1227 cases sent (both initial and follow-up clinical spreadsheets)

886 pathology scoresheets received

742 renal biopsy slides sent to Oxford for review
ITALY: completed cases sent to Oxford: 241
completed cases, slides to be reviewed by I.Roberts: 103

- Rome & Latium: 6 Centers
- Turin & Piedmont: 12 Centers
- Milan & Lombardy: 5 Centers
- Bari & Puglia: 1 Center
- Modena & Emilia: 1 Center
- Verona & Veneto: 1 Center
- 290 to be completed
SWEDEN:
completed cases sent to Oxford: 83

SPAIN:
completed cases sent to Oxford: 78
THE NETHERLANDS:
completed cases sent to Oxford: 35

GREECE:
completed cases sent to: 33

Thessaloniki  Patras  Ioannina: 25
TURKEY:
completed cases sent to Oxford: 43

POLAND:
completed cases sent to Oxford: 31

Istanbul Ankara

Warsow to be completed
Warsow

To be completed:
Katowice and Warsaw: 26
OTHER COUNTRIES: completed cases sent to Oxford:

Total completed cases: 147

- Estonia (Tartu)
- Croatia (Zagreb)
- Germany (Aachen)
- To be completed (UK): 53
Completed cases sent to Oxford

- Italy
- Czech Rep
- Sweden
- Spain
- Turkey
- The Netherlands
- Greece
- Poland
- Estonia
- Croatia
- Germany
To be completed

- Italy
- UK
- Poland
- Greece
- Portugal

- Spain
- Sweden
Completed cases sent to Oxford adults and children <18 years old

N° Cases

<table>
<thead>
<tr>
<th></th>
<th>adults</th>
<th>children</th>
</tr>
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<tbody>
<tr>
<td>Completed cases sent to Oxford</td>
<td>600</td>
<td>100</td>
</tr>
</tbody>
</table>
Follow-up 1 to 20 years

Follow up duration

- Total n of cases
- Follow up > 1 year
- Dialysis before 1 year
Clinical data

First Creat>1.5
Last Creat>1.5
Dialysis
Proposed therapy for IgAN

ACEI and/or ARB
+ steroids (pulses i.v. more effective than oral)
+ azathioprine/cyclophosphamide in progressive forms

Dialysis and Transplantation

Proteinuria and GFR reduction are likely not to be the only markers to early select treatment options for individual patients with IgAN

controls

Proteinuria < 1 g
Macroscopic – microscopic hematuria

Proteinuria > 1 g

GFR reduction
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 “point of no return” when no treatment is effective.

But beside the scientific result, the enthusiastic participation of so many centers in Europe for a spontaneous study, is a valuable result for the scientific community of Nephrologists
VALIGA:
a good platform to launch the Immunonephrology WG of ERA-EDTA

Many thanks
to all the 52 participating Centers from 13 European Countries!!!