SLEuro Training Bursary Programme

- European Lupus Society –

Final Report on Training Program

Lupus Clinic

at

The Centre for Rheumatology

University College London

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Brief preamble

There are probably as many ways of practicing medicine as there are doctors. We are all the result of previous experience – personal and professional - and always a work in progress.

For a young doctor starting a scientific career whilst managing all other clinical responsibilities can be a challenging experience. Additionally, as those interests are often seen as competing against each other by hospital boards and national healthcare systems, the independence of new doctors to explore their scientific interests is curtailed. Frequently, as the scientific structures already in place try to respond to the increasing demands of today's publishing and funding requirements they might sometimes tend to favor already established researchers as a guarantee of continuing activity. This makes for a complex starting point for the young physician-researcher.

This is why training bursaries aimed specifically at young physicians, such as the one from the European Lupus Society, are incredibly important. In the particular case of the SLEuro Training Bursary, the integration of a young researcher in renowned research centres in Systemic Lupus Erythematosus (SLE) from around Europe represents a validation of their research interests. Simultaneously it helps young doctors expand their horizons in the world of academic medicine, by allowing contact with different people and working methods and ethics.

I feel very grateful to have been awarded this bursary by the European Lupus Society to come and work at UCL alongside top academic researchers in SLE.

The centre

The Centre for Rheumatology

The Centre for Rheumatology at UCL is one of the leading academic rheumatology units in the UK. It has several research groups involved in both basic and clinical research in several areas of musculoskeletal diseases. Clinical activity by its members results in thousands of new patients seen and follow-up appointments per year and several sub-specialty clinics that are a national reference.

The Lupus Clinic

A part of the Centre for Rheumatology, the Lupus Clinic has been running since 1979. It is a part of both the British Isles Lupus Assessment Group (BILAG) and Systemic Lupus International Collaborative Clinics (SLICC) group. It is a pioneer in the use of B-cell depletion therapy in the treatment of SLE. It is also recognized by patients (through Lupus UK) as a Lupus Centre of Excellence.

Over the years over 700 SLE patients have been treated here, with over 400 patients under current follow-up. Apart from clinical assessment of SLE patients, the Lupus Clinic also undertakes a systematic and prospective record of BILAG scores and drug history at each visit.

iBLIPS

BLIPS (British Lupus Integrated Prospective System) is, according to the information available on its website, the first Windows program designed for monitoring lupus patients. Developed by ADS-Limathon in close collaboration with the BILAG group, it was launched in 1996 and has since had many iterations, with improvements and additions as both the software and

the BILAG system evolved. Its latest version – v8 – is now online-based, and known as iBLIPS (specifically SilverBLIPS®).

iBLIPS is useful in that it can combine different metrics of interest to lupologists in their daily practice within a single system for data entry, storage and access. It allows for the creation and management of a patient database, and all the necessary assessments – not only activity scoring using BILAG but also damage and QoL assessments, among others. Versions vary, however, according to each centre and their chosen preferences. According to its website it is now used by over 1000 clinical sites in 43 countries, comprising 6200 patients worldwide.

At UCLH the patient database extends from at least 1997 until today. All lupus patients under prospective follow-up at UCLH are included. Demographic information, serial BILAG assessments from each appointment, drug history, immunology data are collected by both the attending physician and specialist nurses who then upload the data into iBLIPS®.

Due to the several revisions of both BILAG and iBLIPS®, as well as staff changes at UCLH, there is some heterogeneity in the way some patient information is input as well as some missing information for various fields across time. Despite the benefits of this excellent system, a complete and comprehensive review across multiple types of assessments and over several years still unfortunately requires a laborious effort of data review and uniformization and prevents complete datasets for most patients with extended follow-up.

The project

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with a heterogeneous phenotypical presentation and evolution, characterized by recurrent acute flares interspersing a chronic evolution. As with other diseases, its global impact and course are difficult to define and no single system of assessment can currently do so perfectly. At present formal patient assessment is mainly based on separate clinical scales for activity and damage. It is up to each individual doctor to combine these, as well as drug history, clinical findings, his knowledge of the patient and his past experiences into “a more global patient assessment”.

TOAD (an acronym for Time, Organ involvement, Activity, Damage) is a novel multimodal system, envisaged by Professor Carlos Vasconcelos, and further advanced by the contributions of Dr Raquel Faria, both at the Unidade de Imunologia Clínica (Clinical Immunology Unit) at Centro Hospitalar e Universitário do Porto, Portugal.

The aim is to obtain both a transverse and cumulative image of the lupus patient, at each point in time. SLE patients are classified according to time with disease (T, in years), organic expression of the disease for the individual patient given in a combination of letters (C – constitutional, S – Skin, A – Articular, B – Blood, K – Kidney, L – Lung, H – Heart, N – Neurologic, O – other), activity status based on the SLEDAI or BILAG score and translated to a clinically relevant category [adapted from the proposed classification by the DORIS taskforce; Roff – remission off drugs (only hydroxychloroquine allowed), Ron – Remission on drugs (steroids less than 6mg/day of prednisone; immunosuppressors allowed if in stable dosage), LUC – Lupus under control ie minimal disease activity on drugs (more than 5mg of prednisone and/or new immunosuppressors), LLDA – Low level disease activity on drugs, AD – active disease, VAD – very active disease)] and overall damage (SLICC damage index - SDI). For each visit a patient would be classified according to each category culminating in a combined TOAD score – for instance,

T:0 O:SAB A:Roff D:0. Over the follow-up, this allows for clinical categorization of the patient according to % of time on a certain level of activity (for instance, 92% Roff).

We believe this classification to be more clinically relevant than using only SLEDAI or BILAG cumulative scores for activity assessment and expect it to aid the follow-up and treatment-to-target objectives of SLE patients followed both by lupologists as well as all other ancillary specialties that aid in the treatment of these patients. A special focus of TOAD interest would be the appropriate selection of SLE patients for inclusion in clinical trials.

Objectives

To validate a new multimodal classification system for SLE patients – TOAD – using patient cumulative data from 2 university hospitals – Centro Hospitalar e Universitário do Porto, in Porto, Portugal, and University College London's Rheumatology Unit, London, United Kingdom.

Outcomes

Cumulative patient data, from the diagnosis of SLE until the last available appointment or until loss-of-follow up was mined from the UCL database in iBLIPS®. Complete data – combining paired assessments of BILAG scores, immunology data and drug history - regarding at least one annual visit for each year of follow-up was available for 90 patients. Drug history regarding biologics (not available on iBLIPS®) was reviewed according to the rituximab and belimumab registries at UCL. Damage scores were calculated after individual patient file review.

The resulting database comprises almost 500 different variables, from demographic to clinical characteristics. Patients from this reference sample were diagnosed at UCL between 1997 and 2010, thus representing up to 22 years of follow-up.

Roughly 9% were male. Ethnic variety is more abundant in the UCL cohort than in Portugal, one of the many reasons that support its use for validation of TOAD. Circa 12% of patients were of African-Caribbean descent, 16.6% of Asian origin (25% of which were Chinese), 47.7% were caucasian, and 23,3% had mixed ancestry.

We believe this sample cohort is well poised to represent damage in the SLE patient population. 6 patients died during follow-up. Median SLICC/ACR Damage Index score was 1 (min 0 – max 6).

31 patients (34% of the patient sample) received rituximab at any given point thus signaling not only a good range of disease activity states (more active, or refractory disease) but also a broader range of therapeutic uses.

Given the amount of clinical and laboratory data accumulated, statistical analysis is still ongoing.

Part of the TOAD model includes categorization of disease activity using criteria based on SLEDAI and drug use (for instance, the DORIS definition of remission on or off therapy, the more recent definition of low level disease activity, etc). Because those criteria were never defined, for the most part, using BILAG for activity scoring, and because SLEDAI and BILAG are not directly comparable, the opinion of the BILAG group (a group of collaborators from multiple centres in the UK) on the appropriate criteria for each activity classification used in TOAD was sought.

Despite the expected difficulties in achieving a trans-system interchangeability an informal consensus produced:

CATEGORY	Definition according to SLEDAI	Definition according to BILAG
Remission	SLEDAI = 0 (or serological activity only) either with no steroids (remission off therapy) or Pred <=5mg per day (remission on therapy)	BILAG D or E in all domains with no steroids (remission off therapy) or Pred <= 5mg per day (remission on therapy)
Lupus under control	SLEDAI = 0 but with Pred > 5mg per day	BILAG C w/ Pred <5mg or D,E in all w/ Pred >5mg
Low level disease activity	0<SLEDAI =< 4 with HCQ and Pred <7,5mg/day, immunosuppression stable Or 0<SLEDAI<=3 on HCQ alone	One or more C and no more than 1 B w/ Pred <7.5mg
Active disease	4 < SLEDAI < 20; (or not fulfilling LLDA criteria)	1B score on Pred > 7.5 OR >=2 B (with possible cap at 2 or 3) AND <=1 A
Very active disease	SLEDAI >= 20	>= 2 A
*HCQ is allowed in all disease activity categories. Stable immunosuppression and biologics are allowed in all categories except remission off therapy.		

Ongoing work

After the two month training programme the trainee will continue to work at UCL/UCLH for an additional month, reviewing the validity and integrity of the database (a continuous necessity given the size of the accumulated data).

Statistical analysis of the resulting data is ongoing. It will involve multivariate analysis and logistic regression looking at the interaction of the 4 variable groups used in TOAD and their role in predicting several outcomes including mortality, damage accrual and response to treatment.

100 patients have already been reviewed in the Portuguese cohort and their statistical analysis is ongoing as well.

Future objectives

The near-future objective is completion of statistical analysis and publication of the results.

In the long term, if the utility of TOAD is effectively suggested by the analysis of this data, we would like to seek further validation of this system and its use in clinical trials.

Queries on the systematic use of TOAD in clinical practice will be sent to doctors who might want to start using it, to assess its ease of use in daily practice and incorporate their suggestions when possible.

Upon TOAD validation in clinical practice an electronic TOAD assessment tool might be created for added ease of use.

Final remarks

It was certainly a very rewarding experience to have come to UCL. SLEuro's bursary was invaluable not only financially but because it established a framework of connections and support that made it easier to achieve my objectives. I would like to thank all in the organization for that.

I am certainly indebted to everyone at UCL's Centre for Rheumatology. Their kindness in welcoming me and helping me along the way was disarming. A special thank you to Prof Anisur Rahman, my supervisor, for always providing a thoughtful solution to obstacles of every nature. His talent for seemingly effortlessly managing so many different people and their projects in his research group is inspiring. I am sure that this leadership might have played its part in forming such a great group of people. Everyone was so unbelievably kind - Thomas, Chris, Filipa, Charlie and Shi-Nan, I cannot thank them enough for always cheering my day either through some great British humour or unmitigated solidarity.