TRAINING BURSARY PROGRAMME REPORT (2021)

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Training bursary programme destination: University of Padua

1) What was the motivation to apply for training in this Centre?

The main motivation to my application to Rheumatology Unit, in Padova University was to have the opportunity to learn from professionals on a recognized European research center in Systemic Lupus Erythematosus (SLE) and could continue the work already started between our rheumatology departments in Italy and Portugal, about SLE flares.
The main objectives of this study were to compare the performance to identify a new flare of SLE disease activity between 4 different instruments: SELENA Flare Index (classic, C-SFI), revised SELENA Flare Index (R-SFI), SLEDAI-2K and SLE-DAS; and to provide construct validity of the SLE-DAS definition of flare.

Retrospective Study

Systemic lupus erythematosus (SLE) is an autoimmune inflammatory chronic disease, with a remitting relapsing course. [1-5] Recent advances in the management of SLE patients are leading to better clinical outcomes and decreased mortality rate. [6] Despite these advances, SLE patients remain at risk of having frequent flares of disease activity. [7] Flare is defined as ”a measurable increase in disease activity in one or more organ systems involving new or worse clinical signs and symptoms and/or laboratory measurements. It must be considered clinically significant by the assessor and usually there would be at least consideration of a change or an increase in treatment’’. [5] Flares are associated with worse prognosis, more hospitalizations, damage accrual, worse quality of life, higher costs and mortality. [1] However, defining a SLE flare remains a challenge, because there is no consensus of how to measure an increase in disease activity. [1, 4] While a conceptual definition for lupus flares was proposed by expert consensus, there is a need for a standardized, operational definition of SLE flares for use in clinical trials, observational studies as well as in clinical practice. [5] Over the years several flare definitions were proposed. [2, 4] The most used disease activity measure in clinical practice is the SLE disease activity index (SLEDAI), which is also a component of the responder indexes applied as primary endpoint in SLE clinical trial (i.e., SRI and BICLA). Using the SLEDAI-2K, flare was defined as an increase of 4 points in the SLEDAI-2K score from the previous visit. [8] However, performance of flare definition based in SLEDAI is limited as it does not account for worsening of previously active features and several important SLE manifestations are not included in this index. [2, 9, 10] The classic SELENA Flare Index (SFI) aimed to improve performance by adding several additional conditions to SLEDAI, including other disease features, worsening in some previously active manifestations, changes in treatment and physician global assessment (PGA).

[9, 11] It further aimed to distinguish severe from mild/moderate flares. However, it does not provide an objective definition of worsening of individual features, the inclusion of changes in treatment and PGA can incur in added subjectivity of flare definition and the definition of severe flares suffer from bias due to the threshold effect (by allowing to count as severe flare an 1 increase of 1 point in SLEDAI, from 12 to 13 points). [11] This tool is currently used as endpoint in clinical trials, but it is not practical nor sufficiently accurate for use in clinical practice. Recognizing the performance limitations of this instrument, its authors devised the Revised Selena Flare Index aiming to improve its accuracy and to allow the distinction between mild and moderate flares. [2] Contrary to the classic SFI, it does not use the SLEDAI and it is inspired in the BILAG, with intention to treat items and a separate analysis of flares by organs systems. [2, 6] The Revised SFI has not yet been adequately validated and is too burdensome to use in clinical practice. The BILAG allows to define flares by organ systems and further categorises mild, moderate, and severe flares. [11] However, the BILAG can miss flares within an organ system, including new or worse severe features (e.g., if a patient has an ongoing severe "A" category in any system, even a new/worse "B" or "A" manifestation in the same system will not be captured as a flare). [9, 11] The BILAG is not frequently used in clinical practice, as it is cumbersome to apply, requiring up to 50 minutes to apply. [9] The SLE Disease Activity Score (SLE-DAS) is a recently developed and validated SLE continuous measure with high sensitivity for changes in disease activity. [10] The optimal discriminative increase in SLE-DAS to detect a clinically meaningful worsening in disease activity was determined by ROC curve analysis to be ≥1.72. In the external validation cohort, it showed a sensitivity of 95.5% and specificity of 98.2% for flares. [10]

2) How the objectives were fulfilled by the training?

During the programme I attended the SLE Outpatient Clinic at RheumatologyDepartment, Padova University. Attending the clinic I have had the opportunity to contact with another organizational model, different from what I am used to, learn new things and exchange experiences with my colleagues. Also, attending the clinic provided me crucial clinical information about patients included in our study and the missing data was completed through the consultation of medical charts. The data collection included: sex; ethnicity (caucasian, other); age (years); age at diagnosis (years); disease duration (years); type of SLE cumulative involvement (yes/no): musculoskeletal, mucocutaneous, renal, haematological, neurological, cardiopulmonary, constitutional, gastrointestinal and antiphospholipid syndrome; immunological cumulative involvement (yes/no): positive antinuclear antibodies, increased anti-double stranded DNA, positive anti-SSA, positive anti-SSB, positive anti- RNP, positive anti-Sm, positive antiphospholipid antibodies, low C3 and/or low C4; SLEDAI-2K score; SLE-DAS score; glucocorticoids dose at baseline (mg/day); hydroxychloroquine (yes/no); immunosuppressive drugs (yes/no): methotrexate, leflunomide, azathioprine, cyclophosphamide, mycophenolate mofetil, cyclosporine, tacrolimus, rituximab, belimumab; and SLICC/ACR Damage index (% with SDI>0).

3) **What are the main opportunities / strengths this centre offers for future applicants?**

The main strengths of the center are: the large experience in treating SLE patients, the large number of SLE patients that we can observe in such short period of time; the friendly work environment to learn and to discuss the project; the close collaboration with Professor Andrea Doria and all his collaborators; the opportunity to attend others connective tissue disease outpatient clinics, the collaborations with other centers and the international recognition of the center, particularly concerning SLE.

4) **Practical advice for future applicants to the SLEuro training bursary**

I would advise the future applicants to have an open mind and a positive attitude to embrace this great experience in order to enjoy the most of it. The time of programme is very short so it is very important to develop the project before the arrival and to 4 schedule everything to guarantee that you can finish the project or at least the things that must be collected and realized on the center on time. You should be prepare to hard work, to focus on that but yet to you shouldn't skip on the opportunity to know other people and other culture during the internship.

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