TITLE: **Pattern of drug use in systemic lupus erythematosus and reasons for drug discontinuation in real life clinical practice**

Background

Systemic lupus erythematosus (SLE) is a chronic immune-mediated inflammatory disease that can lead to premature death. SLE has a relapsing-remitting course, with patients experiencing flares over time. The pharmacological treatment for SLE is aimed at reducing inflammatory activity and minimizing damage. (1) Hydroxychloroquine is the standard treatment for most SLE patients during the entire disease course and conventional immunosuppressants are usually given to those with severe organ involvement. (2) However, a previous study shown that current immunosuppressive strategies seem to be inefficient in providing flare prevention. (3) New biologic agents might be more effective in reducing SLE disease activity and preventing lupus flares but pose challenges regarding appropriate case selection. (4)

Study rational

Medication use in SLE varies widely and therapeutic strategies are well defined only for certain organ manifestations. In clinical practice, the ability to identify the reasons for drug discontinuation and predictors of drug retention is crucial to optimize SLE treatment. So far, no study has tried to identify predictive factors of drug discontinuation in SLE.

Objectives

This study aims to describe patterns of drug use, administration profile, reasons for drug discontinuation and drug retention (for drugs whose continued administration is consensually accepted: Hydroxychloroquine (HCQ), Methotrexate (MTX), Leflunomide (LFN), Azathioprine (AZA), Belimumab) in real world SLE patients.

Primary objective

To assess the pattern of drug use in SLE patients registered in Reuma.pt, the Rheumatic Diseases Portuguese Register.

Secondary objectives

To assess the reasons for discontinuing treatment in SLE patients (lack of efficacy, adverse event, remission, other).

To identify predictive factors of drug retention in SLE patients.

Methods

Study design

We will perform an observational study including SLE patients registered in Reuma.pt, who fulfil ACR and/or SLICC classification criteria.
Information will be retrieved for all patients that have been followed for at least 1 year.

Reuma.pt (www.reuma.pt), the Rheumatic Diseases Portuguese Register, became active in 2008 and includes patients with varied rheumatic diseases from the whole country. A protocol dedicated to SLE patients (Reuma.pt/ LES) became active in September 2012 and by end July

2017 the database includes 1800 lupus patients. Currently several public and private rheumatology clinics contribute on a regular basis to the registry.

Eligibility criteria:

- **Inclusion criteria**:

Patients with SLE diagnosis fulfilling 1997 ACR classification criteria or 2012 SLICC criteria;

Treated with HCQ, systemic glucocorticoids, NSAIDs, immunosuppressive therapies and/or biologic agents;

Age ≥ 18 years;

Having baseline evaluation and follow up information.

- **Exclusion criteria**

Diagnosis of other rheumatic diseases, except secondary antiphospholipid syndrome or secondary Sjogren's syndrome.

Variables to be collected:

Baseline patient characteristics

- Demographic characteristics (gender, age, race, education, smoking, alcohol consumption, BMI);

- Age of diagnosis of SLE;

-Age of onset of SLE symptoms;

- SLE organ involvement;

- Immunological characteristics

- Systemic Lupus Erythematosus Disease Activity Index (SLEDAI);

- Health Assessment Questionnaire (HAQ);

- Physician Global Assessment (PGA);

- C-reactive protein (CRP); erythrocyte sedimentation rate (ESR);

- SLICC-DI;

- Comorbidities;

- Medication: corticosteroids, HCQ, MTX, LFN, immunosuppressants (AZA, Mycophenolate mofetil (MMF), calcineurin inhibitors, Cyclophosphamide (CYC)), biologics (Rituximab, Belimumab) - Starting date of treatment; Doses used; Frequency of administration; stop date and reason for discontinuation.

Follow-up evaluations 3/3 months:

- SLE organ involvement;

- SLEDAI;

- PGA;

- CRP; ESR;

- Medication: corticosteroids, HCQ, MTX, LFN, immunosuppressants (AZA, Mycophenolate mofetil (MMF), calcineurin inhibitors, Cyclophosphamide (CYC)), biologics (Rituximab, Belimumab) - (Starting date of treatment; Doses used; Frequency of administration; stop date and reason for discontinuation).

- **Primary endpoints**:

Patterns of drug use;

Time to discontinuation, by agent (drugs whose continued administration is consensually accepted: HCQ, MTX, LFN, AZA, Belimumab), after adjusting for baseline characteristics and other confounders, using clinical data

- **Secondary endpoints**

Reasons for discontinuation of therapy, by drug;

Variables independently associated with discontinuation of therapy

Analysis plan:

Primary aim

We will perform a descriptive analysis of drug use in SLE. Persistence of therapy (time to discontinuation), by agent (drugs whose continued administration is consensually accepted: HCQ, MTX, LFN, AZA, Belimumab), will be report as the median drug survival time and the probability of maintaining therapy at prespecified time-points. Patients who are loss to follow-up will be censored. The STATA computer software package will be used to analyze the data collected from this study. Continuous variables will be reported as mean +/- standard deviation (or in case of non-normal distribution as median and quartiles). Nominal variables will be displayed as frequency or proportions.

Secondary aims

Patients will be divided according to the reason for discontinuation: lack of response, adverse events, remission, patient's willingness or other reasons. Lack of response will be defined by physician assessment or patients not achieving a 4 point or greater improvement of the SLEDAI score from baseline.
We will use Log rank test to identify which covariates measured at baseline associates with drug discontinuation on univariable analysis. Variables with p-values <0.20 will be included in the multivariable analysis. The Cox regression will be used for the multivariable analysis with forward selection method for model building. The final model will include all variables that retain statistical significance ($p<0.05$).

Limitations and expected results

We hope to identify the pattern of drug use and the main reasons and predictors of discontinuation of therapy in Portuguese patients with SLE. These predictors are expected to improve treatment success since they may contribute to adequate treatment choice according to patient and drug specificities.

Limitations include: Possible information bias due to incomplete filling of the database. Outcome assessment bias, since patient evaluation and database filling are performed by different rheumatologists from multiple Portuguese centers.

Approximate duration of the study

Timelines for the several steps of this project are presented in Table I. Globally, this study will take 8 months to be concluded.

Tabela I	Aug-Oct 2017	Nov-Dec 2017	Jan-Mar 2018
Data extraction	X		
Data analysis		X	
Final report/publication			X

Ethical considerations

This study will be conducted according to the Declaration of Helsinky and the International Guidelines for Ethical Review of Epidemiological Studies. This study will be submitted for validation and approval to the Ethics Committee. Results will be presented in an objective way, and will not be hidden or manipulated.

Research team:

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References:

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