- off-label biologicals such as rituximab and tocilizumab are supported by inconsistent data that leave important questions unanswered; they are most often used in a 'back-against-the-wall' situation.

I25 WHICH IS THE OPTIMAL PRIMARY ENDPOINT FOR LUPUS CLINICAL TRIALS?

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Systemic lupus erythematosus (SLE) causes a wide range of immune-mediated manifestations in most organ-systems. The presentation of SLE is highly heterogeneous in terms of affected systems, type, and severity of disease features, both between- and within- patients over disease course (SLE disease activity). This complexity hinders the development of Clinical Outcome Assessments (COA) for SLE. Lupus clinical trials evaluate the efficacy of drugs that directly reduce or control disease activity through a mode-of-action that modifies immune processes. Clinical expertise is required to identify and quantify appropriately the treatment-related changes in SLE disease activity. Therefore, a Clinician-Reported Outcome Measure (ClinRO) is required as COA for primary assessment of efficacy in SLE clinical trials. Importantly, the primary endpoint in clinical trials should be patient-focused, that is, must be associated with meaningful impact in the main health aspects of importance to patients that are affected by SLE disease activity. Notably, there is an indirect association between how the patients fell and function and SLE disease activity. The primary endpoint for SLE clinical trials should be a precisely defined variable that is cumulatively able to: (1) capture a direct effect of the study drug in changing the SLE disease activity (with a ClinRO); (2) associate with a meaningful (indirect) impact in the patients' main health aspects; (3) be statistically analised to address the research question of drug efficacy in the context of use.

However, the primary endpoints currently used in SLE clinical trials have well recognized limitations that may have hampered the demonstration of efficacy of many promising drugs in SLE clinical trials. These endpoints are defined as a dichotomous response variable obtained through composite responder indexes, namely the SLE Responder Index (SRI) and the British Isles Lupus Assessment Group (BILAG) Composite Lupus Assessment (BICLA), both aggregating the BILAG, the SLE Disease Activity Index (SLEDAI), and the Physician Global Assessment (PGA). Therefore, novel COA are needed to provide an optimal primary endpoint for lupus clinical trials.

The Treatment Response Measure for SLE (TRM-SLE) consortium is in the early phases of a project to develop and validate a novel COA for use in SLE clinical trials.

The SLE Disease Activity Score (SLE-DAS) is a novel, easy to use (http://sle-das.eu/), validated ClinRO COA instrument, with high accuracy and sensitivity to change in SLE disease activity. New evidence with validation of thresholds in the context of clinical trials support the interpretation of the SLE-DAS scores into categories of SLE disease activity and treatment targets. These SLE-DAS score categories are concordant with a wide range of health aspects impacted by SLE assessed in Patient-Reported Outcomes (PRO). Importantly, differences in the SLE-DAS scores are sensitive to clinically meaningful and interpretable changes within patients over time in SLE disease activity and reflect an expected impact on patients' health experiences. There is promising evidence that SLE-DAS is a fit-for-purpose COA and may provide an optimised primary endpoint for lupus clinical trials.

I39 MANAGEMENT OF REFRACTORY APS

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Treatment of thrombosis in patients with antiphospholipid syndrome (APS) is based on long-term oral anticoagulation and treatment of obstetric manifestations on the use of aspirin and heparin. These recommendations are based on randomized controlled trials and observational studies. In detail, patients with definite APS with first venous thrombosis have to be treated with prolonged oral anticoagulation at a target international normalized ratio (INR) of 2.0–3.0. Anticoagulation at INR of 3.0–4.0, isolated antiaggregation, anticoagulation at INR 2.0–3.0 or anticoagulation at INR 2.0–3.0 plus antiaggregation have been proposed for definite APS patients with arterial thrombosis. Regarding obstetric APS, although combined therapy with low-dose aspirin and low-molecular-weight heparin is the mainstay of treatment in women with obstetric APS, the strength of evidence of its efficacy is under discussion.

However, there are many grey areas in the field of APS where the evidence is scarce and where the management of certain patients is difficult. Some examples are patients with "seronegative" APS, those who do not display formal (clinical or laboratory) classification criteria for APS, those with refractory APS despite optimal treatment (recurrent thrombotic events despite optimal anticoagulation or recurrent fetal losses despite the combination of aspirin and low molecular weight heparin), and the treatment of clinical manifestations not included in the classification criteria, such as hematologic manifestations (thrombocytopenia and haemolytic anemia), neurologic manifestations (chorea, myelitis or multiple sclerosis-like lesions), nephropathy and heart valve disease associated with antiphospholipid antibodies. In these cases, the recommendations are based on the common sense since the published evidence is scarce, or it does not exist.

In cases of catastrophic APS, an aggressive treatment is required. Therefore, early diagnosis is very important to start adequate therapy and decrease the high mortality rate of these patients. Once the diagnosis is made or suspected, searching and treating the precipitating factor, mainly infection, is the first step of treatment. The specific therapy of catastrophic APS is the combination of anticoagulation with heparin, and corticosteroids as first line of treatment. Additionally adding intravenous immunoglobulins and/or plasma exchange have to be considered in life-threatening cases. In patients with associated SLE, intravenous cyclophosphamide has demonstrated be beneficial. In refractory cases, rituximab or eculizumab should be added.