

Supplemental Figure Legends

Supplemental Figure 1. Endotypes of SLE. Among the various endotypes, childhood-onset SLE (cSLE), organ-dominant SLE (dermatologic, musculoskeletal -so called 'rhubus'-, renal, neurological, hematologic), lupus with antiphospholipid syndrome (SLE-APS) and Sjögren's syndrome (SS) have received more attention due to differences in prognosis and treatment. Rheumatoid arthritis, APS and SS can also exist as primary, autonomous diseases.

Supplemental Figure 2. Clinical course in SLE. Approximately 70% of SLE patients follow a relapsing-remitting course, with the rest 30% divided equally between prolonged remission and persistently active disease. Prolonged remission for at least two consecutive years has been associated with halting of damage accrual in Caucasian SLE patients.

Supplemental Figure S3 Management of proliferative (class III-IV) lupus nephritis. Initial treatment in proliferative lupus nephritis usually consists of low-dose intravenous CY or MMF, both combined with glucocorticoids (pulses of intravenous methylprednisolone, then oral prednisone 0.3-0.5 mg/kg/day). Combination of MMF with a CNI, especially TAC, is an alternative in cases with nephrotic-range proteinuria, while patients at high-risk for a poor outcome may also be treated with high-dose CY. The target of therapy ("response") is a reduction in proteinuria by $\geq 25\%$ with stable GFR at first 3 months; $\geq 50\%$ in proteinuria by 6 months; and $< 0.5-0.7$ g/24hr proteinuria at 12. If these targets are reached, subsequent long-term maintenance treatment with MMF or AZA should follow, with no or low-dose (< 7.5 mg/day) glucocorticoids. In non-responding disease or in relapses, a repeat kidney biopsy may be considered. Treatment options include rituximab, switching to an alternative induction therapy, or adding TAC to MMF.

AZA, azathioprine; GC, glucocorticoids; IV-CY, intravenous cyclophosphamide; MMF, mycophenolate mofetil; TAC, tacrolimus

Supplemental Figure S4 Management of membranous (class V) lupus nephritis. Immunosuppressive treatment in class V LN is recommended from baseline in cases with nephrotic-range proteinuria, or in cases where renin-angiotensin-aldosterone blockade fails to lower proteinuria to less than 1000 mg/24h within 3-12 months. MMF is the treatment of choice due to its favourable efficacy/toxicity ratio, while CY and CNIs are alternative options. The target of therapy and the therapeutic options in non-responding or relapsing disease, are generally the same as in proliferative LN.

CNI, calcineurin inhibitor; GC, glucocorticoids; IV-CY, intravenous cyclophosphamide; MMF, mycophenolate mofetil; RAAS, renin-angiotensin-aldosterone blockade; UPr, urinary protein

Supplemental Figure S5 Diagnostic approach and management of possible neuropsychiatric systemic lupus erythematosus. Attribution of neuropsychiatric manifestations to SLE requires a comprehensive, multidisciplinary approach to exclude mimics, with consideration of both “favouring” factors (such as type and timing of manifestation, presence of generalized, non-neurological disease activity, abnormal neuroimaging and cerebrospinal fluid analysis, positive aPL antibodies, as well as confounding factors suggestive of alternative diagnoses. If “primary NPSLE” is suspected, immunosuppressive therapy is recommended for presumed inflammatory manifestations, while anticoagulation/antiplatelet therapy for manifestations presumed to be thrombotic or embolic; combination of both may be considered if both mechanisms are potentially operant.

aPL, antiphospholipid antibodies; CNS, central nervous system; CSF, cerebrospinal fluid analysis; MRI, magnetic resonance imaging of brain and/or spine that includes T1, T2, FLAIR, and diffuse-weighted imaging protocols; NPSLE, neuropsychiatric systemic lupus erythematosus

Supplemental Figure S6 Management of autoimmune thrombocytopenia in systemic lupus erythematosus. Autoimmune thrombocytopenia in SLE warrants treatment when platelet number falls below 20-30,000/mm³, following exclusion of non-immune causes of thrombocytopenia. Acute treatment consists of glucocorticoids (methylprednisolone pulses are recommended to avoid starting with a high prednisone dose PO) with or without intravenous immunoglobulin (the latter usually reserved for patients with active bleeding or contraindications to glucocorticoids). The target is a safe -and not necessarily normal- platelet count. Early institution of glucocorticoid-sparing agents is advisable, because therapy is often protracted. Rituximab is recommended in case of relapse, due to its additional established efficacy in idiopathic immune thrombocytopenia. Splenectomy or thrombopoietin agonists should be reserved as “rescue” therapy in cases refractory to aforementioned treatments.

AZA, azathioprine; APS, antiphospholipid syndrome; CsA, cyclosporine A; GC, glucocorticoids; IS, immunosuppressive; IVIG, intravenous immunoglobulin; IV MP intravenous methylprednisolone; MMF; mycophenolate mofetil; PLTs, platelets; Pre, prednisone; TMA, thrombotic microangiopathy; TPO, thrombopoietin