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Review Article

Summary of 2019 EULAR Guidelines for Treatment of Systemic Lupus Erythematosus

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Abstract
SLE is a common rheumatological disease with variable presentations and life-threatening organ involvement, associated with comorbidities and mortality. Many diseases can mimic clinical picture of lupus and treatment strategies are based on many factors including age, pregnancy, comorbidities, toxicities of the drugs and other factor. A clear step wise approach regarding various organ specific issues is helpful. EULAR guidelines are very useful for initiating, stepping up or stepping down the treatment for such cases.
This review summarizes the recently updated 2019 EULAR Guidelines for lupus patients with an aim to help manage the lupus more efficiently for better disease control and prevent complications.
Key Words: SLE treatment, EULAR guidelines for lupus, Organ specific SLE treatment.

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Introduction

SLE (Systemic Lupus Erythematosus) is a multisystem disease with challenging management due to its variable presentations, organ threatening complications, comorbidities & increased mortality. Complex treatment regimens are often needed to manage such cases. As many new therapeutic options had been added in the recent past, there was a very strong need for evidence-based international guidelines to better manage lupus cases with the safest possible therapeutic options. Every patient needs a tailored treatment specific to his/her clinical presentation of lupus in the light of life choices, comorbidities, and drug-related side effects. The treating physicians need a clear and concise approach about initiation titrating up or deaccelerating the treatment plan, especially when there is severe organ involvement or cases with disease refractory to treatment options.

Recently updates European League Against Rheumatic Disease (EULAR) guidelines 2019 for SLE are clinically very helpful for the physicians to manage the disease presentations' diversities.

Remission and Low Disease Activity:

The following definitions are important to understand for the standardization of treatment goals.

Complete remission is zero disease activity without glucocorticoid (GC) and Immunosuppressive drugs (IS).[1]

Low disease activity means a Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score of <3 on antimalarials, OR SLEDAI score <4 and Physician Global Assessment (PGA) <1 with GC <7.5mg/day and IS without any side effects.[2]

Complete renal remission: proteinuria <500 mg /24 hours and serum creatinine within 10% of baseline.

Partial renal remission: more than 50% reduction in proteinuria to sub nephrotic range and serum creatinine within 10% of baseline within 6-12 months of starting the treatment.[3]

Flare: measures any increase in disease activity, which needs a change of treatment. Risk factors for flares include disease onset at a young age, no use of antimalarials, disease activity persistence, low complements, and high titre of anti-double stranded DNA antibodies (anti-dsDNA).[4,5]

Drugs Used to Treat SLE:

Hydroxychloroquine (HCQ):

HCQ is recommended for all lupus cases as it reduces disease activity and also reduces flare-ups. A recommended maximum daily dose is 5mg/kg/day (real body weight is used to calculate the dose).[6] Retinal toxicity is 10% after 20 years of continuous use, and it

is dose and duration-dependent.[7] In addition to being immunomodulator, it also reduces thrombotic tendency, osteoporosis, and disease progression. Renal failure or pre-existing retinal/macular disease also increases the risk. Its considered safer in pregnancy. Dose reduction is needed for severe renal or hepatic disease. Drug levels can be monitored for compliance, but there is insufficient data for this recommendation.[6] Quinacrine, another antimalarial, can be used if there is retinal toxicity or cutaneous issue.[8]

Glucocorticoid (GC):

Due to many side effects of GC when used in high doses (>7.5mg/day) for a longer duration, it should be kept on a daily dose of less than 7.5mg /day or should be stopped when possible.[9] The following options can achieve this: either the use of immunosuppressive agents (IS) at early stage or use of pulse Methylprednisolone (MP) at the start, which may allow for a lower dose and fast tapering of oral GC.[6] Acute organ threatening disease such as lupus nephritis, neuropsychiatric lupus, etc., is often managed by using high dose intravenous MP (250-1000mg/day for three days). It's important to exclude infections before using high dose MP.[10]

Immunosuppressive (IS) Drugs:

Choice of IS drugs depends on the organ involved, the severity of the disease, comorbidities and age, fertility and pregnancy concerns, side effects, cost, and availability. If GC and HCQ are not enough to control the disease, the next options are methotrexate (MTX) or azathioprine (AZA). The teratogenic effect of MTX makes AZA a better choice for use in females of reproductive age. Mycophenolate is stronger and superior immunosuppressive agent than AZA and MTX, and it works both for renal and extrarenal lupus (except neuropsychiatric lupus), but it's teratogenic and more costly[6,11]. Cyclophosphamide (CYC) is used for organ threatening disease, refractory disease, or only as a rescue option for non-organ threatening refractory disease. CYC has strong Gonadal toxicity, which makes it less favourable in the reproductive age group. Concomitant use of GnRH analogies or ovarian/ sperm cryopreservation should be considered for reproductive age patients.[12] Cancers and infection risk of CYC are also an important aspect to be kept in mind. Calcineurin inhibitors (CNi) such as Tacrolimus can also be considered for lupus nephritis (LN) or haematological issues.[13]

Biological agents (BA):

Belimumab should be used for extrarenal diseases, which is inadequately controlled by a combination of HCQ, GC with or without IS (especially those with SLDAI>10, Prednisolone requirement >7.5 mg/day, low complement, high anti dsDNA). It works better for cutaneous, serological, and musculoskeletal symptoms.[14]

Patients with disease refractory to IS and/or Belimumab can be treated with Rituximab (RTX) or when these drugs are contraindicated. More than one immunosuppressive therapy should have failed before trying RTX (except for autoimmune thrombocytopenia or hemolytic anemia, where RTX is efficacious even for non-lupus cases).[6,15] Lupus nephritis (LN) patients who failed to respond to the first line IS (CYC, MMF) or who have a relapse, RTX can be used[16].

Organ-Specific Treatment for SLE

Skin Disease in Lupus:

Skin biopsy is needed for atypical or refractory cases. Sunscreen and smoking cessation are important[17]. The following regimen is recommended in order of preference: topical agents (GC &/or CNi) and HCQ. Systemic GC for the shortest possible dose and duration may be added when needed. Quinacrine can replace HCQ if there is retinal toxicity. Those who don't respond to the first line (almost 40% of cases) may need MTX. Other options for such cases include retinoids, dapsone, MMF,[6]. Thalidomide is effective, but due to its significant toxicities (teratogenicity, neuropathy, and relapses on discontinuation), it's mainly used as a rescue drug for treatment failure with multiple agents. Belimumab and RTX can also help in refractory cases.[17,18]

Neuropsychiatric SLE (NPSLE):

Inflammatory disease is treated by GC &/or IS, whereas aPL related disease needs antiplatelet & anticoagulants. A combined approach for patients who have coexistence of both the process. SLE cases with stroke should be treated as non-SLE stroke cases.[6] Immunosuppressive therapy may be needed if stroke patients are negative for aPL and other risk factors for atherosclerosis or those who have recurrent events. Symptom control is an additional requirement, e.g., antipsychotic drugs for psychosis.[19]

Detailed assessment, including non-neurological disease activity assessment, neuroimaging, CSF analysis, and aPL, is needed to ascertain the underlying pathology, and sometimes it's may not be easy to do so. Exclusion of other possible diagnoses such as atherosclerotic disease, infections & cancers must be ruled out[20].

Haematological manifestations and SLE:

Thrombocytopenia is the commonest issue and managed with moderate/high dose GC (preferably pulse MP) plus IS agents for lupus thrombocytopenia (platelet count <30,000/mm^3). CNi has the least marrow suppression effect, whereas MMF, MTX, AZA & CYC can significantly increase myelotoxicity. The

next option is IVIG (intravenous immunoglobulins) for those with an inadequate response to GC & IS.[6] Those with no response (failure to raise platelet count >50,000/mm^3) or relapse, RTX, or CYC should be considered. Thrombopoietin agonist or splenectomy are the last options.[21] Autoimmune hemolytic anemia follows the same principles regarding GC, IS, and RTX.[22] Leucopenia is common but rarely needs treatment after the exclusion of other causes.[6]

Lupus Nephritis

Vigilant monitoring is important, especially for those at high risk of renal disease (male, early age onset lupus, low complements, high titer positive antibodies such as dsDNA, anti C1q, persistent systemic disease).[23] Diagnosis should be established by biopsy, and treatment started with induction, followed by maintenance. Second kidney biopsy may be considered for incomplete response to treatment after one year. CYC and MMF are the first choices for induction. Low dose CYC has lesser gonadotoxicity and comparable efficacy to high dose CYC. A high dose is recommended for those with an increased risk of progression to end-stage renal disease (ESRD). Maintenance therapy is MMF (more effective) or AZA (less toxic and safer for pregnancy) depending on age, comorbidities, race & plan for pregnancy.[6] RTX is needed for refractory or relapsing cases despite being on CYC or MMF.[24]

CNi such as Tacrolimus can be used as second line agents either alone or in combination with other IS such as MMF for induction or maintenance in cases with membranous LN, podocytopathy, or proliferative GN with refractory nephrotic syndrome. Monitoring renal functions and blood levels of CNi is important to avoid drug-related nephropathy.[25]

Antiphospholipid Antibodies (aPL) & Antiphospholipid Syndrome (APS) in SLE

Patient with SLE should be tested for APS as these can have thrombotic and obstetric complications. Lupus related APS should be managed as primary APS. During high-risk periods such as pregnancy or post-operative, the patient may receive additional anticoagulation such as low molecular weight heparin (LMWH). However, NOAC should not be used for secondary prevention (except in cases with a low-risk aPL profile and no arterial thrombosis who have difficulty using LMWH or warfarin).

It's not clear that Primary prophylaxis with low dose aspirin should be given to lupus cases with any aPL antibodies or only to those for high-risk aPL profile (triple aPL positive, Lupus Anticoagulant or high titer of anti-cardiolipin antibodies).[6,26]

Other Common Issues in SLE

Infections in SLE

A proactive approach to detect and treat infections is needed in SLE cases as they are at high risk due to drugs used and disease-related factors.[10] Vaccinations should be done according to EULAR recommendations for patients with rheumatological diseases, especially for influenza, pneumococcus and human papilloma virus.[6]

CVS Risk stratification in SLE

Patients with SLE can suffer more from heart attack and strokes. Hence management of cardiovascular risk factors such as diabetes, hypertension, hyperlipidaemia is essential. Both lupus and its therapies are risk factors for CVS diseases (GC use, persistent disease, Lupus nephritis, aPL). Routine use of statin is not recommended but should be considered based on lipid profile and other risk factors for atherosclerosis.[6] Calculation of 10-year CVD risk using SCORE is recommended[27]. Routine use of aspirin for primary prophylaxis may be considered but should be viewed in risk of bleeding hazard.[28]

Discussion & Conclusion

Organ threatening complications of Lupus (e.g., severe lupus nephritis, neuropsychiatric lupus etc) needs induction therapy (CYC, MMF), followed by maintenance therapy with MMF or AZA, [Table 1]. Failed induction cases will need upgrading to biological drugs[23-25]. Infections are very common and proactive approach for prevention, early detection and aggressive treatment is important. CVS risk factors should be aggressively addressed[10,27,28]. Complications such as Thrombotic Thrombocytopenic Purpura (TTP), pulmonary haemorrhages, hyper gammaglobulinemia, and the disease resistant to biological therapy may need plasmapheresis / IVIG and other additional measure[23-25]. SLE cases with haematological manifestations such as cytopenia may benefit from Prednisolone, CNi, IVIG, RTX. Drugs such as MTX, AZA, CY can cause significant myelotoxicity[15,16].

Mild to moderate disease without organ involvement can be managed well with HCQ, low dose GC and MTX (or AZA). In addition, non-organ threatening refractory disease also sometime pose a challenging clinical situation and may need strong immunosuppressants such as CYC or even biological drugs. Pregnancy or a plan to conceive is an important consideration and the drugs which are relatively safer in pregnancy includes: HCQ, AZA in low dose, Prednisolone and IVIG.[6,8,11,13]

There have been many advances in the treatment of SLE along with new evidence about effectiveness and toxicities of the various therapies (including two biological agents along with CNi) to manage this complex multisystem disease. In addition, as we are

aware of the fact that SLE presents with a variable severity of the disease presentations, these 2019 updated guidelines by EULAR were much needed to provide a stepwise, evidence based and systematic approach for upgrading or downgrading the treatment.

Abbreviations: AZA (Azathioprine), BILAG (British Isles Lupus Assessment Group), CNi (Calcineurin Inhibitor), CYC (Cyclophosphamide), GC (Glucocorticoids), HCQ (Hydroxychloroquine), IS (immunosuppressive), IV (Intravenous), IVIG (Intravenous Immunoglobulins), MMF (Mycophenolate Mofetil), MTX (Methotrexate), PO (Per Oral), RA (Rheumatoid Arthritis), SLEDAI (Systemic Lupus Erythematosus Disease Activity Index), RTX (Rituximab),TTP (Thrombotic Thrombocytopenic Purpura).

Table 1: *Summary of the Treatment*

Severity	Criteria	Drug therapies
Mild	Constitutional symptoms, mild arthritis, rash <9%, Platelet 50000-100000/mm3, SLDAK6, BILAG C manifestations.	HCQ (may add PO GC). Second line MTX/AZA.
Moderate	RA like arthritis, rash 9-18%, cutaneous vasculitis <18%, platelet counts 20000- 50000, serositis, SLEDAI 7- 12, BILAG B manifestations.	HCQ+GC (Oral/IV) +IS (MTX/AZA). Second line is MMF /CNi/CYC.
Severe	Organ involvement (nephritis, cerebritis, pneumonitis, systemic vasculitis), platelet count <20000, SLEDAI>12, UP, Hemophagocytic syndrome, BILAG A manifestations.	HCQ+GC (Oral /IV) + IS Inductions (MMF, CYC) Maintenance (MMF/AZA) Second line (Belimumab, RTX) Refractory: IVIG, Plasmapheresis.

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