Myanmar Rheumatology Society

Management of Systemic Lupus Erythematosus

Updated 07.08.2020

Systemic lupus erythematosus (SLE) is autoimmune connective tissue disease affecting multisystem with a broad spectrum of clinical presentations involving almost every organ and system.

1. Classification Criteria

Either Revised ACR 1987 criteria (1997 update) or SLICC 2012 or ACR-EULAR2017 criteria can be used to diagnose SLE.

1.1. ACR 1987 criteria (1997) update (4 out of 11 criteria)

1.	Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2.	Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or clinician observation
3.	Discoid rash	Erythematosus raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
4.	Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a clinician
5.	Arthritis	Nonerosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6.	Serositis	Pleuritis – Convincing history of pleuritic pain or rubbing heard by a clinician or evidence of pleural effusion OR Pericarditis – Documented by ECG, rub, or evidence of pericardial effusion
7.	Renal disorder	Persistent proteinuria greater than 500 mg/24 hours or greater than 3+ if quantitation not performed OR cellular casts – May be red cell, hemoglobin, granular, tubular, or mixed

8.	Neurologic disorder	Seizures OR psychosis – In the absence of offending drugs or known metabolic derangements
9.	Hematologic disorder	**Hemolytic anemia** – With reticulocytosis OR Leukopenia – Less than 4000/mm3 total on 2 or more occasions OR Lymphopenia – Less than 1500/mm3 on 2 or more occasions OR Thrombocytopenia – Less than 100,000/mm3 (in the absence of offending drugs)
10.	ANA	An abnormal titer of ANA by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome
11.	Immunologic disorders	Anti-DNA – Antibody to native DNA in abnormal titer OR Anti-Sm – Presence of antibody to Sm nuclear antigen OR Positive antiphospholipid antibody on: An abnormal serum level of IgG or IgM anticardiolipin antibodies OR A positive test result for lupus anticoagulant using a standard method ORA false-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test

1.2. SLICC criteria (2012)

The SLICC criteria for SLE classification requires: 1) Fulfillment of at least four criteria, with at least one clinical criterion AND one immunologic criterion OR 2) Lupus nephritis as the sole clinical criterion in the presence of ANA or anti-dsDNA antibodies. Criteria are cumulative and need not be presently concurrently

1.	Acute cutaneous lupus	Lupus malar rash (do not count if malar discoid); bullous lupus; toxic epidermal necrolysis variant of SLE; maculopapular lupus rash; photosensitive lupus rash (in the absence of dermatomyositis); OR subacute cutaneous lupus (nonindurated psoriaform and/or annular polycyclic lesions that resolve without scarring, although occasionally with postinflammatory dyspigmentation or telangiectasias)
2.	Chronic cutaneous lupus	Classic discoid rash; localized (above the neck); generalized (above and below the neck); hypertrophic (verrucous) lupus; lupus panniculitis (profundus); mucosal lupus; lupus erythematosus tumidus; chilblains lupus; OR discoid lupus/lichen planus overlap
3.	Non scarring alopecia	Diffuse thinning or hair fragility with visible broken hairs (in the absence of other causes)
4.	Oral or nasal ulcers	Palate, buccal, tongue, OR nasal ulcers (in the absence of other causes)
5.	Joint disease	Synovitis involving 2 or more joints, characterized by swelling or effusion OR Tenderness in 2 or more joints and at least 30 minutes of morning stiffness
6.	Serositis	Typical pleurisy for more than 1 day, pleural effusions, or pleural rub, OR Typical pericardial pain (pain with recumbency improved by sitting forward) for more than 1 day, pericardial effusion, pericardial rub, or pericarditis by electrocardiography in the absence of other causes
7.	Renal	Urine protein-to-creatinine ratio (or 24-hour urine protein) representing 500 mg protein/24 hours, OR Red blood cell casts
8.	Neurologic	Seizures; psychosis; mononeuritis multiplex (in the absence of other known causes, such as primary vasculitis); myelitis; peripheral or cranial neuropathy (in the absence of other known causes; OR acute confusional state (in the absence of other causes)
9.	Hemolytic anemia	Hemolytic anemia

10.	Leukopenia or lymphopenia	Leukopenia (<4000/mm3 at least once) (in the absence of other known causes) OR Lymphopenia (<1000/mm3 at least once) (in the absence of other known causes)
11.	Thrombocytopenia	Thrombocytopenia (<100,000/mm3) at least once in the absence of other known causes)
12.	ANA	ANA level above laboratory reference range
13.	Anti-dsDNA	Anti-dsDNA antibody level above laboratory reference range (or >2-fold the reference range if tested by ELISA)
14.	Anti-Sm	Presence of antibody to Sm nuclear antigen
15.	Antiphospholipid	Antiphospholipid antibody positivity as determined by any of the following: Positive test result for lupus anticoagulant; false-positive test result for rapid plasma reagin; medium- or high-titer anticardiolipin antibody level (IgA, IgG, or IgM); or positive test result for anti-beta 2-glycoprotein I (IgA, IgG, or IgM)
16.	Low complement	Low C3; low C4; OR low CH50
17.	Direct Coombs test	Direct Coombs test in the absence of hemolytic anemia

1.3. EULAR/ACR classification criteria (2019)

A patient was classified as having SLE if they had a positive ANA ≥1:80 and had ≥10 points. Within each domain, only the highest weighted criterion is counted toward the total score.

Clinical and laboratory criteria are catergorized separately.

No.	Manifestation	Type	Point	Type	Point	Type	Point
1.	Renal	Class 3/4 nephritis	10	Class 2 / 5 nephritis	8	Proteinuria ≥0.5 g/day	4
2.	Mucocutaneous	ACLE	6	SCLE or DLE	4	Alopecia or oral ulcers	2
3.	Serosa	Pericarditis	6	Effusion	5		

4.	Musculoskeletal	Arthritis	6				
5.	Central Nervous system	Seizure	5	Psychosis	3	Delirium	2
6.	Constitutional	Fever	2				
7.	Blood	AIHA/ATP	4	Leucopenia	3		
8.	Complement	Low C3 and C4	4	Low C3 or C4	3		
9.	Specific antibodies	Anti-Sm or Anti-dsDNA	6				
10.	Antiphospholipid	Anyone	2				

2. Case Definitions

Lupus nephropathy (ACR)

LN is defined as clinical and laboratory manifestations that meet ACR criteria (persistent proteinuria >0.5 gm per day or spot urine protein/creatinine ratio of > 0.5 or greater than 3+ by dipstick, and/or "active urinary sediment" (>5 RBCs/ high-power field [hpf], > 5 white blood cells [WBCs]/hpf in the absence of infection, or cellular casts limited to RBC or WBC casts).

Disease activity

For the purpose of planning appropriate treatment, disease activity (extra-renal) has been broadly categorized as mild, moderate or severe.

	Mild activity	Moderate activity	Severe activity
SLEDAI	<6	6-12	>12
General	fatigue	fever	

Mucocutaneous	malar rash, diffuse alopecia, mouth ulcers,	lupus-related rash up to 2/9 body surface area, cutaneous vasculitis, alopecia with scalp inflammation	Rash involving > 2/9 body surface area, severe digital vasculitis with impending gangrene
Musculoskeletal	arthralgia, myalgia	arthritis	severe symptomatic myositis
Haematology	Platelets 50-149 x 109/l	platelets 25-49 x109/l	platelets <25x109/l
Serositis		pleurisy, pericarditis	severe pleurisy and/or pericarditis with effusion,ascites
CVS			Myocarditis , endocarditis
GI		hepatitis	enteritis
CNS			myelopathy, psychosis, Acute confusion, optic neuritis

Severe disease is defined as organ or life threatening and reflects the most serious form of systemic disease that requires potent immunosuppression.

Renal response (EULAR-EDTA) (KDIGO)

Complete renal response	urine protein: creatinine ratio (UPCR) <50 mg/mmol (roughly equivalent to proteinuria <0.5 g/24 h) and normal or near-normal (within 10% of normal GFR if previously abnormal) GFR
Partial renalresponse	≥50% reduction in proteinuria to subnephrotic levels and normal or near-normal GFR, should be achieved preferably by 6 months and no later than 12 months following treatment initiation
Non-responder or Treatment failure (6-month response)	those who do not achieve either complete or partial response after 6 month of induction therapy

Renal Flares (EULAR)

Nephritic flares	reproducible increase of serum creatinine by ≥30% (or, decrease in GFR by ≥10%) and active urine sediment with increase in glomerular haematuria by ≥10 red blood cells per high power field, irrespective of changes in proteinuria
Proteinuric flares	reproducible doubling of UPCR to >100 mg/mmol after complete response or reproducible doubling of UPCR to >200 mg/mmol after partial response

3. Treatment

3.1. Treatment of non-organ threatening lupus i.e. mild to moderate disease activity

3.1.1. **Mild disease activity**

Prednisolone- 20mg/day for 1-2 weeks and taper gradually + Hydroxychloroquine

± Methotrexate-7.5-15mg/week

OR

± leflunomide 20 mg per day

NSAID should be given as necessary

3.1.2. **Moderate disease activity**

Prednisolone 0.5 mg/day for 2-4 weeks and taper gradually

(If necessary Pulse IVI Methylprednisolone 250 mg for 1-2days can be given)

And HCQ 6.5 mg/kg/day (200 mg per day should work)

And Azathioprine 1.5 -2.0mg/kg/day or MTX 10- 20 mg/week or MMF 1-2g/day or leflunomide 20 mg/ day or ciclosporin 2.0mg/kg/day or tacrolimus 1-4mg per day in 2 divided doses

3.2. Severe disease activity – Intensive therapy

3.2.1. Indications for intensive therapy

3.2.1.1. Renal indications

1. Confirmed proteinuria of ≥1.0 g per 24 hours (either 24-hour urine specimens or spot protein/ creatinine ratios are acceptable
2. Combinations of the following, assuming the findings are confirmed in at least 2 tests done within a short period of time and in the absence of alternative causes:
    i. Proteinuria≥0.5 gm per 24 hours plus hematuria, defined as ≥5 RBCs per hpf or cellular casts or initial rising creatinine
    ii. Proteinuria ≥0.5 gm per 24 hours plus extra-renal manifestations

Renal biopsy should be considered if renal involvement is suspected.

If initial creatinine is >300 umol/L, patient should be referred to nephrologist.

3.2.1.2.Extra-renal indications

1. Neuropsychiatric SLE (NPSLE) - cerebritis, myelopathy, optic neuritis, mononeuritis multiplex, severe peripheral neuropathy
2. Organ-threatening vasculitis – retinal vasculits, mesenteric vasculitis, coronary vasculitis, severe digital vasculitis with impending gangrene
3. Myocarditis, severe pericarditis with impending cardiac temponade
4. Severe interstitial lung disease
5. Severe symptomatic myositis
6. Lupus gut- Enteropathy
7. Haematological involvement- Severe autoimmune haemolytic anaemia

3.2.2. Intensive therapy

2 phases –

1. Induction therapy
2. Maintenance therapy

Phase I- Induction therapy (Month 1-6)

2 options- monthly CYC regimen (or) Daily MMF regimen

Monthly CYC regimen

Month 1

IVI methylprednisolone 500mg OD x 3 days

IVI CYC 400 to 600 mg OD for 1 day

+

IVI equivalent dose of Mesna (400 or 600 mg)

Month 2-6

IVI CYC for 400 to 600 mg OD for 1 day

+

IVI equivalent dose of Mesna

Throughout 6 month period- tapering dose of prednisolone or equivalent dose of methylprednisolone; start with 1mg/kg/day for one month, and tapered gradually monthly.

e.g

Body weight	≤ 40kg	>40 kg	> 40kg	>40 kg
	Prednisolone-5mg tablet	methylprednisolone	Prednisolone-5mg tablet	methylprednisolone
Month-1	8 tablet OD	16 mg bd	10 tablet OD	16 mg tds
Month-2	4 tablet OD	16 mg od	6 tablet OD	16 mg 1:1/2
Month-3	3 tablet OD	12 mg od	4 tablet OD	16 mg OD
Month-4	2 tablet OD	8 mg od	3 tablet OD	12 mg OD
Month-5	1.5 tablet OD	6 mg od	2 tablet OD	8mg OD
Month-6	1 tablet OD	4 mg od	1tablet OD	4mg OD

Daily MMF regimen

Month-1

Initial Pulse IVI methylprednisolone 500mg OD x 3 days

Throughout 6 month period-

tapering dose of prednisolone or equivalent dose of
methylprednisolone as above
+
PO MMF 1.5 to 2g/day

Phase II- Maintenance therapy (for those who respond to induction therapy)

One of following four options can be used.

1. MMF 1-1.5g/day (preferred option if the patient has partial response after 6 month induction therapy)
2. Azathioprine (start with 25mg/day and titrate up monthly up to max dose 75mg/day)
3. Leflunomide 20mg/day
4. Three monthly IVI CYC regimen

Maintenance therapy should be at least 3 to 5 years.

Lowest possible dose of steroid which can control the disease activity should be used.

3.3.Treat to target

It is suggested to attain mild disease activity or remission and to prevent the disease flare

3.4. Adjunct treatment in patients with LN

a. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers are indicated for patients with proteinuria (UPCR >50 mg/mmol) or hypertension.
b. Cholesterol lowering with statins is indicated for persistent dyslipidaemia (target lowdensity lipoprotein (LDL)-cholesterol 2.58 mmol/litre (100 mg/dl))
c. Hydroxychloroquine is recommended to improve outcomes by reducing renal flares and limiting the accrual of renal and cardiovascular damage

d. Acetyl-salicylic acid in patients with anti-phospholipid antibodies
e. Calcium and vitamin D supplementation
f. Immunizations with non-live vaccines (Hepatitis B vaccination, yearly Influenza vaccine, 5-yearly pneumococcal vaccine)

4. Monitoring and prognosis of LN

a. Active LN should be regularly monitored by determining at each visit body weight, blood pressure, serum creatinine and eGFR, serum albumin, proteinuria, urinary sediment (microscopic evaluation), complete blood cell count and ESR.
b. (Serum C3 and C4, serum anti-dsDNA antibody if possible.)
c. Lipid profile should be measured at baseline and monitored intermittently.
d. Anti-phospholipid antibodies should be repeated in 12 weeks' time if raised.
e. Visits should be scheduled every 4 weeks for the first 6 months after diagnosis or flare, and then according to the response to treatment. Monitoring for renal and extra-renal disease activity should be lifelong at least every 3–6 months interval.

5. Lupus and pregnancy

a. Pregnancy may be planned in stable patients with inactive lupus and UPCR <50 mg/ mmol or 24 hr Urinary proteinuria <0.5G/day, for the preceding 6 months, with GFR that should preferably be >50 ml/min.
b. The following medications must be stopped before planning the pregnancy.

    Leflunomide -2-years

    MTX -3- 6months

    CYC -3-6months

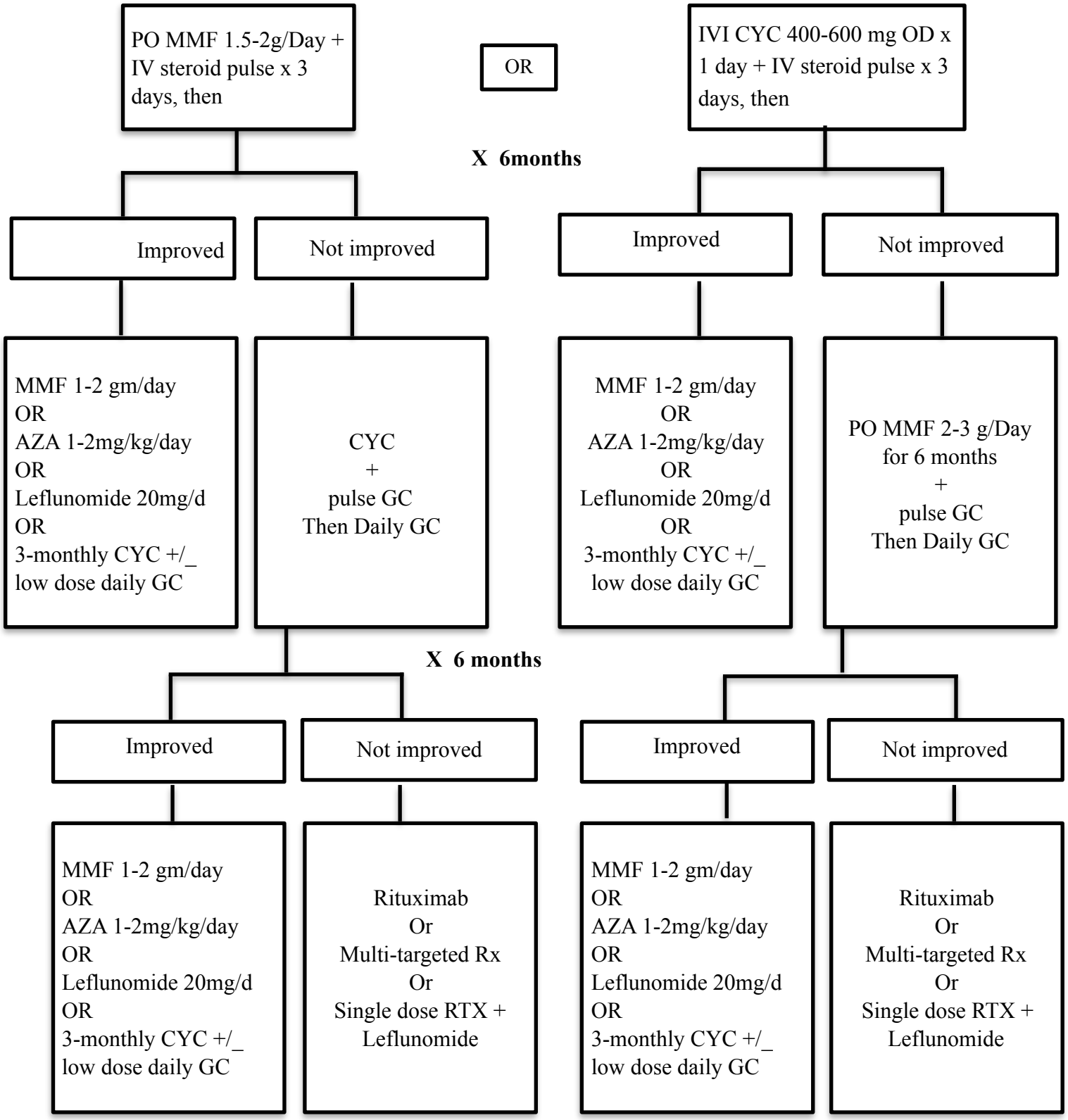
    MMF -3-6 months

c. Acceptable medications include hydroxychloroquine, and where needed, low dose prednisone, azathioprine and/or calcineurin inhibitors.
d. The intensity of treatment should not be reduced in anticipation of pregnancy.

e. During pregnancy, acetylsalicylic acid should be considered to reduce the risk of preeclampsia.
f. Patients should be assessed at least every 4 weeks, preferably by a specialist physician and obstetrician.
g. Flare of LN during pregnancy can be treated with acceptable medications stated above depending on severity of flare.

6. Lupus activity and tuberculosis

1. In case of miliary tuberculosis, tuberculous meningitis, smear positive pulmonary TB and extensive parenchymal lesions on CXR, intensive therapy should preferably be started after completion of 2-month initial phase of anti-TB therapy. Meanwhile the disease activity will be controlled with low-to-moderate dose steroids and hydroxychloroquine.
2. If the lupus activity is very severe and organ or life threatening, intensive therapy might be started after 2-week of anti-TB initiation.


PO MMF 1.5-2g/Day + IV steroid pulse x 3 days, then
OR
IVI CYC 400-600 mg OD x 1 day + IV steroid pulse x 3 days, then
X 6months
Improved
Not improved
Improved
Not improved
MMF 1-2 gm/day
OR
AZA 1-2mg/kg/day
OR
Leflunomide 20mg/d
OR
3-monthly CYC +/_
low dose daily GC
CYC
+
pulse GC
Then Daily GC
MMF 1-2 gm/day
OR
AZA 1-2mg/kg/day
OR
Leflunomide 20mg/d
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AZA 1-2mg/kg/day
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Leflunomide 20mg/d
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3-monthly CYC +/_
low dose daily GC
Rituximab
Or
Multi-targeted Rx
Or
Single dose RTX +
Leflunomide

6. Shared care in SLE (Primary health care level))

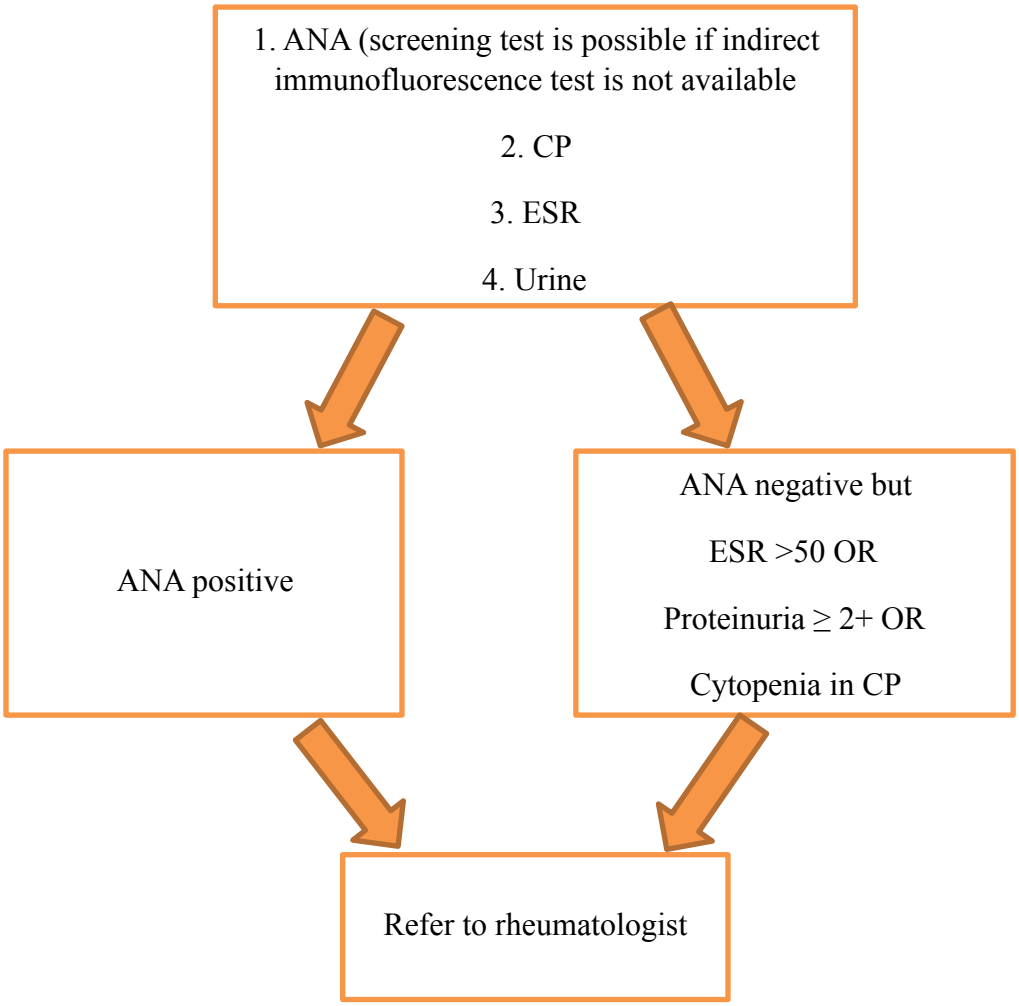
1. When to suspect SLE

1.1. Suspected clinical features from classification criteria OR

1.2. Atypical features in one system (eg., young stroke) OR

1.3. Involvement of more than one system

2. What to do when SLE is suspected



3. Continue care and indications for refer back to Rheumatologist

CR, ESR, ALT, Creatinine, Urine RE should be monitored at follow up.

A.

- CP- cytopenia except mild degree of anaemia OR
- ESR >50 OR
- ALT ≥ 2 times upper limit of normal OR
- Creatinine > upper limit OR
- Urine RE- active urinary sediments or hematuria or pyuria or proteinuria ≥ 1+

Refer back to rheumatologist to escalate immunosuppression

B.

If the results are acceptable but current steroid dose is prednisolone ≥7.5 mg/day or methyl prednisolone ≥ 6mg/day, *refer back to rheumatologist to adjust steroid dose.*

C.

- Red flag signs in SLE
- Cough ≥ 3 weeks
- Fever ≥ 2 weeks
- Vasculitic rash on palms and tip of toes
- New onset edema

Refer back to rheumatologist

D.

If the results are acceptable and current steroid dose is prednisolone <7.5 mg/day or methyl prednisolone < 6mg/day, *continue current treatment* and repeat CP,ESR, ALT, creatinine and urine RE after 3 months and review the patient.

4. Management of minor infection

Patients can be managed at primary health care for following minor infections

A. Non severe GE without features of sepsis

B. Upper respiratory tract infection

C. Lower UTI (eg, cystitis)

D. Minor skin infection

- For above infections, treat infection appropriately, correct fluid and electrolyte imbalance and advice adequate and balanced nutrition.
- Continue current dose of steroid (Steroid should not be stopped abruptly)
- Withold DMARDS (eg, methotreaxate, leflunomide, azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus) until infection is resolved.