REVIEW ARTICLE

AN OSTEOPATHIC APPROACH TO THE MANAGEMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS

Alexander M. Hoelscher, DO[1]; Gretchen Sonnenberg, DO[1]; Meng Smith, DO[1]; Derek Fritz, DO[1]; Annie Belanger, DO[1]; Royce Toffol, DO[2]

[1]Peak Vista Community Health Centers–Family Medicine Residency, Colorado Springs, CO
[2]Peak Vista Community Health Centers, Colorado Springs, CO

KEYWORDS

Osteopath

Corticosteroids

Hydroxychloroquine

Immunosuppressants

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease that primarily affects women and people of Hispanic, African, and Asian descent. The treatment goals are similar to other autoimmune diseases: preventing progressive damage to organs and decreasing disease activity to increase patient quality of life. Steroids can lead to rapid control of symptoms but have many long-term side effects; patients should be transitioned to steroid-sparing agents and new biologics when possible. Special populations require specific considerations, such as those experiencing renal or neuropsychiatric symptoms or drug side effects or those who are pregnant or planning to conceive. Sustained remission is very difficult to achieve, and current guidelines recommend targeting a low SLE activity state to optimize quality of life. An osteopathic approach to managing SLE attempts to reflect the principles of osteopathy into evidence-based medicine to optimize quality of life.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multi-organ progressive autoimmune disease that affects young women more often than men and is more prevalent and severe in people of Hispanic, African, and Asian descent.[1–3] The clinical features of SLE are variable across individuals and evolve throughout a patient's lifetime.[4] This makes management challenging and requires flexibility and vigilant monitoring. Management considerations require an evaluation of illness, comorbidities, and patient goals. Although SLE remains poorly understood, the prognosis of SLE is relatively good, with the 10-year survival rate improving over the past several decades to almost 90%.[5,6] Although survival rates and quality of life continue to improve, SLE can lead to permanent damage in one or more organ systems.[7] Joint and skin manifestations of SLE are most common; renal, hematologic, and neurologic manifestations are most damaging.[8] To maximize the quality of life in patients with SLE, treatment should focus on achieving minimal disease activity, rather than complete remission. Additional focuses should include minimizing drug toxicity, preventing organ damage, and educating patients about their role in disease management.[9,10] Because SLE increases the risk of atherosclerosis, smoking cessation, counseling on diet, and statin therapy should also be considered.[11]

CORRESPONDENCE:
Alexander M. Hoelscher, DO | markhoelscher@outlook.com

ISSN: 1877-573X doi:10.33181/13098

DISEASE EVALUATION

Prior to determining the appropriate treatment modality, disease activity and severity must be assessed by clinical evaluation. The goal of clinical evaluation is to differentiate new disease from chronic damage, to differentiate SLE from coexisting conditions, and to assess for adverse reactions to treatment.[12] A baseline evaluation should include a comprehensive physical examination and labs to assess renal status, drug toxicities, and disease activity. Laboratory evaluation should include complete blood count (CBC), acute phase reactants, urinalysis, urine protein-to-creatinine ratio, serum creatinine, estimated glomerular filtration rate (eGFR), double-stranded DNA (dsDNA), and complement levels (C3, C4). Antibody titers may not need to be repeated, with the exception of dsDNA and complement.[13] If renal disease is suspected, a renal biopsy should be performed for further evaluation.[14–18]

In addition to a physical exam and labs, the SLEDAI-2K score is a useful tool to incorporate into the clinical evaluation (table 1). The SLEDAI-2K score is used as a predictor of mortality and as a measure of disease activity; it can guide current therapy by describing changes in disease activity from one visit to the next.[19] Osteopathic physicians can utilize their ability to assess the patient for somatovisceral dysfunctions and viscerosomatic dysfunctions that can arise as complications of SLE. By monitoring for these dysfunctions, the physician will have a further assessment of the progress of the disease and the ability to tailor aspects of treatment to address somatic dysfunctions.

TABLE 1:
SLEDIAK-2K score for clinical evaluation of SLE

1. Seizure?	13. Pyuria?
2. Psychosis?	14. Proteinuria?
3. Organic brain syndrome?	15. Rash?
4. Visual disturbance?	16. Mucosal ulcers?
5. Cranial nerve disorder?	17. Pleurisy?
6. Lupus headache?	18. Pericarditis?
7. CVA?	19. Low complement?
8. Vasculitis?	20. Increased DNA binding?
9. Arthritis?	21. Fever?
10. Myositis?	22. Thrombocytopenia?
11. Urinary casts?	23. Leukopenia?
12. Hematuria?	24. Alopecia?

GENERAL PHARMACOLOGICAL TREATMENT

While the body is capable of self-regulation, to an extent, the current expert recommendation is that lupus treatment should be built around antimalarials for chronic control, and clinicians should expect lupus patients to be on these medications for life unless there are hard contraindications to their use.[20–22] When initiating treatment, hydroxychloroquine (HCQ) should be the preferred maintenance treatment unless it is contraindicated.[23]

In addition to maintenance treatment of SLE with HCQ, glucocorticoids are the current treatment of choice for rapid control of acute or life-threatening manifestations of SLE.[24] Alternative therapies are emerging through novel immunomodulators which may avoid the side effects of corticosteroids.[25] Rituximab (RIX) is a monoclonal antibody directed against the CD20 antigen on the surface of B lymphocytes and is available for use in patients with severe or refractory manifestations of the disease, but its efficacy is uncertain.[26–28]

TREATMENT OF CUTANEOUS LUPUS

Photosensitivity is a common finding in many subtypes of SLE (table 2). Ultraviolet light (UV) injury can cause skin lesions to develop that may persist for months. Therefore, physicians should encourage patients to wear sunscreen and counsel them to avoid medications that can cause photosensitivity, such as thiazide diuretics, neuroleptics, and tetracyclines.[29]

Cutaneous lupus erythematosus (CLE) includes discoid lupus, subacute cutaneous lupus (SCLE), and acute cutaneous lupus (ACLE).[30] Typical locations include the face, neck, and head. It is diagnosed clinically, with a biopsy to confirm.[30] There are currently no FDA-approved treatments; therefore, the recommended treatment of mild or limited disease includes smoking cessation, avoidance or protection from UV exposure, and topical treatments.[31] Topical therapies include steroids or calcineurin inhibitors. If the disease is refractory to topical therapies, HCQ or chloroquine (CQ) can be initiated.[32] For severe disease refractory to topical/HCQ/CQ therapy, additional quinacrine therapy is initiated followed by methotrexate (MTX).[32] Thalidomide, retinoids, dapsone, and mycophenolate mofetil (MMF) may also be used for second-line treatment. Other therapeutic options may be cost-limited in their approach.[32,33]

Both ACLE and SCLE are rare and manifest as extreme photosensitivity that begins as a papular eruption or small scaly plaques that transform into annular or psoriasiform lesions.[31] While ACLE is associated with active SLE, SCLE can be caused by commonly utilized monoclonal antibody therapies.[34] Cessation of offending drugs is an effective treatment for both, with the treatment of SLE proving helpful in the resolution of ACLE.[30] Similar to CLE, first-line therapy for SCLE includes topical steroid use and avoidance of UV exposure. Ustekinumab has also been suggested as a therapeutic option in refractory or combined SCLE autoimmune disease pathologies.[35] There is a significant lack of high-quality evidence for SCLE therapies, although clinical trials are underway for Janus kinase 1 inhibitors.[34]

TREATMENT OF MUSCULOSKELETAL MANIFESTATIONS

Arthralgias are common in patients with SLE, and osteopathic physicians have the ability to use many modalities to address musculoskeletal manifestations. Nonsteroidal anti-inflammatory drugs (NSAIDs) are also particularly effective for musculoskeletal symptoms, serositis, and headaches; however, their safety is often of concern.[36] Nonsteroidal anti-inflammatory drugs have an increased risk of acute renal failure, cutaneous and allergic reactions, hepatotoxicity, and aseptic meningitis in patients with SLE.[36] Methotrexate remains an excellent choice for control of arthritic manifestations.[37] Belimumab can reduce autoantibody levels in SLE, and may be indicated as an add-on therapy for skin and musculoskeletal manifestations in patients without severe lupus nephritis or active central nervous system lupus.[38,39]

Osteopathic physicians also have the ability to utilize osteopathic manipulative treatment (OMT) to return the body to normal alignment in cases of nondeforming myalgias and arthritis.[40] Studies also show there could be benefits of OMT in conditions that commonly coexist in patients with lupus, such as fibromyalgia.[41–44] However, physicians should remain aware of the limitations of OMT in SLE, such as high-velocity/low-amplitude (HVLA), due to the increased risk of osteopenia and osteoporosis from chronic steroid use, inactivity from chronic pain, and as a direct result of the disease.[45,46]

TREATMENT OF RENAL MANIFESTATIONS

Lupus nephritis is a complex and broadly differentiated manifestation of lupus that has a high mortality and morbidity.[47] It is often discovered in baseline labs. Patients should be screened for proteinuria, serum creatinine and estimated GFR, microscopic hematuria, and hypertension. A renal biopsy can assess disease activity and properly classify the subtype of lupus nephritis, although some consider this controversial because initial treatment is generally the same: MMF and corticosteroids.[47] Others state that repeat renal biopsies can be performed to assess for response to treatment, and standard therapy regimens depend on the subtype of lupus nephritis, plans for pregnancy, and response to initial therapy. A renal transplant may be necessary if lupus nephritis progresses despite standard treatment.[18] Belimumab may help decrease proteinuria in patients with

proteinuria of more than 1,000 mg/g (113 mg/mmol) creatinine despite standard treatment.[39,48]

Known renal manifestations or other end-organ involvement, may need to be followed at 3-month intervals or sooner.[49] Due to the possibility of clinically silent laboratory abnormalities, patients with low disease states should be followed between 3- and 6-month intervals.[50,51] Earlier treatment, absence of mucocutaneous, renal, or hematologic involvement, and the use of immunosuppressive therapy are associated with mild or lower disease activity.[52]

TREATMENT OF PSYCHIATRIC MANIFESTATIONS

Osteopathic physicians are uniquely trained to appreciate the high incidence of depression in those affected by chronic diseases, such as SLE.[53,54] There are also primary psychiatric changes due to SLE, known as neuropsychiatric systemic lupus erythematosus.[55] These symptoms can be vague, such as memory issues and behavioral changes, which may mask the diagnosis of SLE.[56] It requires independent therapeutic management, depending on severity, after other causes have been excluded.[57] Cognitive behavioral therapy (CBT), which relies on both behavioral remodeling and cognitive restructuring to change disruptive thought patterns, is most commonly utilized.[58] Depression, fatigue, and substance abuse complicate all aspects of care, and physicians should consider screening patients frequently and utilizing available resources as needed.

TREATMENT OF DRUG-INDUCED LUPUS

The osteopathic pillar of metabolism-nutrition considers factors that may affect the self-regulatory and self-healing mechanisms of the body from a dietary standpoint. For example, the management of SLE can be augmented by applying osteopathic philosophy and whole person care. Consider the impact of lifestyle changes on disease burden.[59,60] Regular exercise, a healthy diet high in vegetables and lean meats, smoking cessation, sun avoidance, optimizing mental health, and vitamin D supplementation should be recommended.[59]

As another example, drug-induced lupus erythematosus (DILE) is a lupus-like syndrome triggered by specific medications in some individuals, with studies suggesting genetically related susceptibility.[61] Well-documented drug triggers include sulfonamides, procainamide, hydralazine, isoniazid, methyldopa, minocycline, phenytoin, and tumor necrosis factor-alpha inhibitors. Treatment goals for this model include promoting energy conservation by balancing the body's energy expenditure and exchange, thereby enhancing immune system function. For DILE, then, treatment is the identification and cessation of the offending medication.[62]

TREATMENT CONSIDERATIONS IN PREGNANCY

As active SLE or SLE flares during pregnancy have been associated with an increased risk of both premature birth and fetal mortality, pregnancy in patients with SLE is considered a high-risk pregnancy.[63–65] Patients considering conception should be maintained on medications that are compatible with pregnancy. Hydroxychloroquine is safe and effective in pregnancy, has been documented to successfully prevent flares, and decreases the risk of thrombosis, preeclampsia, and congenital heart block.[66,67]

It is a general recommendation that pregnancy should be delayed until the disease has been in remission for 6 months, as serological activity at the time of conception is associated with an increased risk of disease flares during pregnancy and puerperium.[64,68] Before they conceive, patients with SLE should be assessed for current disease activity, drug use, medical disorders, autoantibody profile, and previous obstetrical history.[69] This should include screening for the following antibodies: anti-Ro (SSA), anti-La (SSB), antiphospholipid, lupus anticoagulant, anticardiolipin, anti-Beta2 glycoprotein 1, free T4, and TSH.[70]

Anti-Ro levels have a direct correlation with congenital heart disease and neonatal lupus syndrome.[71] Anti-Ro/SSA-positive pregnant patients should be monitored by serial fetal echocardiography starting at the 16th week of pregnancy.[72] Anticoagulants and aspirin should be considered in patients with positive antiphospholipid antibodies.[69] Of the antiphospholipid antibodies, the lupus anticoagulant is the only one to be proven to predict pregnancy loss.[73] While the kidneys are the most likely organ system to worsen in pregnancy, it may be difficult to differentiate between lupus nephritis and preeclampsia.[65,67]

Fetal monitoring should screen carefully for placental insufficiency and appropriate fetal growth in the third trimester.[69] During pregnancy, women should also be monitored for thyroid disease, which is associated with an increased risk of preterm birth and miscarriage and is a common comorbidity of SLE.[74] A

TABLE 2:
Management of cutaneous manifestations of SLE

THERAPY OPTIONS

	MILD/ LIMITED	WIDESPREAD/ MODERATE	REFRACTORY
CLE	Topical steroids/ calcineurin inhibitors Preventive measures	HCQ/CQ	Quinacrine addition MTX addition Thalidomide, retinoids dapsone, and MMF
ACLE	Topical steroids/ calcineurin inhibitors Preventive measures Cessation of offending agent Treatment of underlying SLE	More aggressive treatment of underlying SLE Further investigation of offending agent Question differential diagnosis	More aggressive treatment of underlying SLE Further investigation of offending agent Question differential diagnosis

*Currently under further clinical investigation.

THERAPY OPTIONS CONT.

	MILD/ LIMITED	WIDESPREAD/ MODERATE	REFRACTORY
SCLE	Cessation of offending agent Preventative measures Topical steroids/ calcineurin inhibitors	More aggressive treatment of underlying SLE Further investigation of offending agent Question differential diagnosis	Ustekinumab* Janus kinase 1 inhibitors*
DILE	Cessation of offending agent	Cessation of offending agent	

TABLE 3:
Lifestyle interventions in SLE

FURTHER OSTEOPATHIC CONSIDERATIONS

SLE PATIENTS ARE PRONE TO	WHAT TO DO FOR SLE PATIENTS	WHAT TO AVOID IN SLE PATIENTS
Accelerated atherosclerosis	Balanced diet, smoking cessation, statin as needed[11]	
Arthralgia and other associated symptoms	Physical therapy, osteopathic manipulative therapy, exercise[75]	High-velocity, low-amplitude technique
Depression	CBT, psychiatrist trained in SLE, frequent screening for mood changes and substance abuse	
Fatigue	Exercise, healthy diet, CBT	Lack of sleep, overexertion
Increased risk of infection	Stay up to date on vaccinations (inactivated vaccines such as PCV13 and PPSV23).[76–79] Personal protective equipment. Counseling that immunizations may be less effective.	
Low vitaminD/ osteopenia/ osteoporosis	Check vitamin D levels; supplement as needed[80]	Chronic steroid use
Photosensitivity	Broad-spectrum sun protection	
Hematologic changes	Monitor and treat infection[12]	

CONCLUSION

Systemic lupus erythematosus is a multi-organ progressive autoimmune disease with manifestations that vary by person. Disease severity can be classified clinically by the SLEDAI-2K, which then can guide osteopathic treatment that considers body unity, self-regulation, and the interrelationship of structure and function together. There are many unique challenges facing those experiencing renal or neuropsychiatric symptoms or drug side effects and those who are pregnant or planning to conceive. Current guidelines, which are frequently updated as new medical advances are found, currently suggest targeting a low SLE activity state, as sustained remission is difficult to achieve. Osteopathic physicians can help facilitate a low SLE activity state by not only employing guideline-recommended treatment, but also integrating osteopathic screening tools and treatment into the care of the patient for an encompassing treatment plan that addresses the patient as a whole, and not just as a disease. Lastly, osteopathic physicians are encouraged to remain conscientious of the burden of chronic disease on their patients, and treatment goals should focus on decreasing disease activity and severity to optimize quality of life.

REFERENCES

1. Systemic Lupus Erythematosus (SLE). October 18, 2018. Accessed December 17, 2022. https://www.cdc.gov/lupus/facts/detailed.html
2. Weckerle CE, Niewold TB. The unexplained female predominance of systemic lupus erythematosus: clues from genetic and cytokine studies. *Clin Rev Allergy Immunol*. 2011;40(1):42–49. doi:10.1007/s12016-009-8192-4
3. Barbhaiya M, Feldman CH, Guan H, et al. Race/ethnicity and cardiovascular events among patients with systemic lupus erythematosus. *Arthritis Rheumatol*. 2017;69(9):1823–1831. doi:10.1002/art.40174
4. Hill DD, Eudy AM, Egger PJ, Fu Q, Petri MA. Impact of systemic lupus erythematosus disease activity, hydroxychloroquine and NSAID on the risk of subsequent organ system damage and death: analysis in a single US medical centre. *Lupus Sci Med*. 2021;8(1):e000446. doi:10.1136/lupus-2020-000446
5. Gordon C. Long-term complications of systemic lupus erythematosus. *Rheumatology*. 2002;41(10):1095–1100. doi:10.1093/rheumatology/41.10.1095
6. Doria A, Iaccarino L, Ghirardello A, et al. Long-term prognosis and causes of death in systemic lupus erythematosus. *Am J Med*. 2006;119(8):700–706. doi:10.1016/j.amjmed.2005.11.034
7. Kyttaris VC. Systemic lupus erythematosus: from genes to organ damage. *Methods Mol Biol*. 2010;662:265–283. doi:10.1007/978-1-60761-800-3_13
8. Petri M. Treatment of systemic lupus erythematosus: an update. *Am Fam Physician*. 1998;57(11):2753–2760. Accessed December 17, 2022. https://www.aafp.org/pubs/afp/issues/1998/0601/p2753.html
9. van Vollenhoven RF, Mosca M, Bertsias G, et al. Treat-to-target in systemic lupus erythematosus: recommendations from an international task force. *Ann Rheum Dis*. 2014;73(6):958–967. doi:10.1136/annrheumdis-2013-205139

10. Bertsias G, Ioannidis JPA, Boletis J, et al; Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics. EULAR recommendations for the management of systemic lupus erythematosus. Report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics. *Ann Rheum Dis*. 2008;67(2):195–205. doi:10.1136/ard.2007.070367

11. Schoenfeld SR, Kasturi S, Costenbader KH. The epidemiology of atherosclerotic cardiovascular disease among patients with SLE: a systematic review. *Semin Arthritis Rheum*. 2013;43(1):77–95. doi:10.1016/j.semarthrit.2012.12.002

12. Lam NCV, Ghetu MV, Bieniek ML. Systemic lupus erythematosus: primary care approach to diagnosis and management. *Am Fam Physician*. 2016;94(4):284–294. Accessed December 17, 2022. https://www.aafp.org/pubs/afp/issues/2016/0815/p284.html

13. Raissi TC, Hewson C, Pope JE. Repeat testing of antibodies and complements in systemic lupus erythematosus: when is it enough? *J Rheumatol*. 2018;45(6):827–834. doi:10.3899/jrheum.161365

14. Vilá LM, Alarcón GS, McGwin G Jr, Bastian HM, Fessler BJ, Reveille JD; LUMINA Study Group. Systemic lupus erythematosus in a multiethnic cohort (LUMINA): XXIX. Elevation of erythrocyte sedimentation rate is associated with disease activity and damage accrual. *J Rheumatol*. 2005;32(11):2150–2155. Accessed December 17, 2022. https://www.jrheum.org/content/jrheum/32/11/2150.full.pdf

15. Barnes EV, Narain S, Naranjo A, et al. High sensitivity C-reactive protein in systemic lupus erythematosus: relation to disease activity, clinical presentation and implications for cardiovascular risk. *Lupus*. 2005;14(8):576–582. doi:10.1191/0961203305lu2157oa

16. Ortega LM, Schultz DR, Lenz O, Pardo V, Contreras GN. Review: Lupus nephritis: pathologic features, epidemiology and a guide to therapeutic decisions. *Lupus*. 2010;19(5):557–574. doi:10.1177/0961203309358187

17. Lefkowith JB, Gilkeson GS. Nephritogenic autoantibodies in lupus: current concepts and continuing controversies. *Arthritis Rheum*. 1996;39(6):894–903. doi:10.1002/art.1780390605

18. Fanouriakis A, Kostopoulou M, Cheema K, et al. 2019 Update of the Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of lupus nephritis. *Ann Rheum Dis*. 2020;79(6):713–723. doi:10.1136/annrheumdis-2020-216924

19. Gladman DD, Ibañez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. *J Rheumatol*. 2002;29(2):288¬–291. Accessed December 18, 2022. https://www.jrheum.org/content/29/2/288.long

20. Fox RI. Mechanism of action of hydroxychloroquine as an antirheumatic drug. *Semin Arthritis Rheum*. 1993;23(2)(suppl 1):82–91. doi:10.1016/s0049-0172(10)80012-5

21. McKeon KP, Jiang SH. Treatment of systemic lupus erythematosus. *Aust Prescr*. 2020;43(3):85–90. doi:10.18773/austprescr.2020.022

22. Basta F, Fasola F, Triantafyllias K, Schwarting A. Systemic lupus erythematosus (SLE) therapy: the old and the new. *Rheumatol Ther*. 2020;7(3):433–446. doi:10.1007/s40744-020-00212-9

23. Wallace DJ. Antimalarial agents and lupus. *Rheum Dis Clin North Am*. 1994;20(1):243–263. Accessed December 18, 2022. https://www.ncbi.nlm.nih.gov/pubmed/8153401

24. Amissah-Arthur MB, Gordon C. Contemporary treatment of systemic lupus erythematosus: an update for clinicians. *Ther Adv Chronic Dis*. 2010;1(4):163–175. doi:10.1177/2040622310380100

25. Parker BJ, Bruce IN. High dose methylprednisolone therapy for the treatment of severe systemic lupus erythematosus. *Lupus*. 2007;16(6):387–393. doi:10.1177/0961203307079502

26. Rovin BH, Furie R, Latinis K, et al. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. *Arthritis Rheum*. 2012;64(4):1215–1226. doi:10.1002/art.34359

27. Merrill JT, Neuwelt CM, Wallace DJ, et al. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial. *Arthritis Rheum*. 2010;62(1):222–233. doi:10.1002/art.27233

28. Smith MR. Rituximab (monoclonal anti-CD20 antibody): mechanisms of action and resistance. *Oncogene*. 2003;22(47):7359–7368. doi:10.1038/sj.onc.1206939

29. Millard TP, Hawk JL, McGregor JM. Photosensitivity in lupus. *Lupus*. 2000;9(1):3–10. doi:10.1177/096120330000900103

30. Okon LG, Werth VP. Cutaneous lupus erythematosus: diagnosis and treatment. *Best Pract Res Clin Rheumatol*. 2013;27(3):391-404. doi:10.1016/j.berh.2013.07.008

31. Little AJ, Vesely MD. Cutaneous lupus erythematosus: current and future pathogenesis-directed therapies. *Yale J Biol Med*. 2020;93(1):81–95. Accessed December 18, 2022. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7087060/

32. Chasset F, Francès C. Current concepts and future approaches in the treatment of cutaneous lupus erythematosus: a comprehensive review. *Drugs*. 2019;79(11):1199–1215. doi:10.1007/s40265-019-01151-8

33. Schultz HY, Dutz JP, Furukawa F, et al. From pathogenesis, epidemiology, and genetics to definitions, diagnosis, and treatments of cutaneous lupus erythematosus and dermatomyositis: a report from the 3rd International Conference on Cutaneous Lupus Erythematosus (ICCLE) 2013. *J Invest Dermatol*. 2015;135(1):7–12. doi:10.1038/jid.2014.316

34. Bolton C, Chen Y, Hawthorne R, et al. Systematic review: monoclonal antibody-induced subacute cutaneous lupus erythematosus. *Drugs R D*. 2020;20(4):319–330. doi:10.1007/s40268-020-00320-5

35. Mazgaj M, Picard-Dahan C, Deschamps L, Marinho E, Estève E, Descamps V. Successful ustekinumab treatment in a patient with psoriasis and subacute cutaneous lupus erythematosus. *Int J Dermatol*. 2020;59(4):e118–e120. doi:10.1111/ijd.14773

36. Ostensen M, Villiger PM. Nonsteroidal anti-inflammatory drugs in systemic lupus erythematosus. *Lupus*. 2000;9(8):566–572. doi:10.1191/096120300678828794

37. Gansauge S, Breitbart A, Rinaldi N, Schwarz-Eywill M. Methotrexate in patients with moderate systemic lupus erythematosus (exclusion of renal and central nervous system disease). *Ann Rheum Dis*. 1997;56(6):382–385. doi:10.1136/ard.56.6.382

38. Srivastava A. Belimumab in systemic lupus erythematosus. *Indian J Dermatol*. 2016;61(5):550–553. doi:10.4103/0019-5154.190107

39. Plüß M, Tampe B, Niebusch N, Zeisberg M, Müller GA, Korsten P. Clinical efficacy of routinely administered belimumab on proteinuria and neuropsychiatric lupus. *Front Med. 2020*;7:222. doi:10.3389/fmed.2020.00222

40. Cojocaru M, Cojocaru IM, Silosi I, Vrabie CD. Manifestations of systemic lupus erythematosus. Maedica. 2011;6(4):330–336. Accessed December 18, 2022. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3391953

41. Gamber RG, Shores JH, Russo DP, Jimenez C, Rubin BR. Osteopathic manipulative treatment in conjunction with medication relieves pain associated with fibromyalgia syndrome: results of a randomized clinical pilot project. *J Am Osteopath Assoc*. 2002;102(6):321–325. Accessed December 18, 2022. https://www.ncbi.nlm.nih.gov/pubmed/12090649

42. Marske C, Bernard N, Palacios A, et al. Fibromyalgia with gabapentin and osteopathic manipulative medicine: a pilot study. *J Altern Complement Med*. 2018;24(4):395–402. doi:10.1089/acm.2017.0178

43. Dardzinski JA, Ostrov BE, Hamann LS. Myofascial pain unresponsive to standard treatment: successful use of a strain and counterstrain technique with physical therapy. *J Clin Rheumatol*. 2000;6(4):169–174. doi:10.1097/00124743-200008000-00001

44. Cicchitti L, Martelli M, Cerritelli F. Chronic inflammatory disease and osteopathy: a systematic review. *PLoS One*. 2015;10(3):e0121327. doi:10.1371/journal.pone.0121327

45. Sen D, Keen RW. Osteoporosis in systemic lupus erythematosus: prevention and treatment. *Lupus*. 2001;10(3):227–232. doi:10.1191/096120301671413439

46. What people with lupus need to know about osteoporosis. Accessed August 18, 2022. https://www.bones.nih.gov/health-info/bone/osteoporosis/conditions-behaviors/osteoporosis-lupus

47. Almaani S, Meara A, Rovin BH. Update on lupus nephritis. *Clin J Am Soc Nephrol*. 2017;12(5):825–835. doi:10.2215/CJN.05780616

48. Pavkov ME, Collins AJ, Coresh J, Nelson RG, et al. Kidney disease in diabetes. In: Cowie CC, Casagrande SS, Menke A, et al., eds. *Diabetes in America*. 3rd ed. National Institute of Diabetes and Digestive and Kidney Diseases (US); 2018. TABLE 22.1, Albuminuria Categories According to KDIGO Classification. Accessed December 18, 2022. https://www.ncbi.nlm.nih.gov/books/NBK568002/table/ch22.tab1/

49. Fanouriakis A, Kostopoulou M, Alunno A, et al. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. *Ann Rheum Dis*. 2019;78(6):736–745. doi:10.1136/annrheumdis-2019-215089

50. Gladman DD, Ibañez D, Ruiz I, Urowitz MB. Recommendations for frequency of visits to monitor systemic lupus erythematosus in asymptomatic patients: data from an observational cohort study. *J Rheumatol*. 2013;40(5):630–633. doi:10.3899/jrheum.121094

51. Guidelines for referral and management of systemic lupus erythematosus in adults. American College of Rheumatology Ad Hoc Committee on Systemic Lupus Erythematosus Guidelines. *Arthritis Rheum*. 1999;42(9):1785–1796. doi:10.1002/1529-0131(199909)42:9<1785::AID-ANR1>3.0.CO;2-#

52. Ugarte-Gil MF, Wojdyla D, Pons-Estel GJ, et al. Predictors of remission and low disease activity state in systemic lupus erythematosus: data from a multiethnic, multinational Latin American cohort. *J Rheumatol*. 2019;46(10):1299–1308. doi:10.3899/jrheum.180433

53. Navarrete-Navarrete N, Peralta-Ramírez MI, Sabio-Sánchez JM, et al. Efficacy of cognitive behavioural therapy for the treatment of chronic stress in patients with lupus erythematosus: a randomized controlled trial. *Psychother Psychosom*. 2010;79(2):107–115. doi:10.1159/000276370

54. Sarwar S, Mohamed AS, Rogers S, et al. Neuropsychiatric systemic lupus erythematosus: a 2021 update on diagnosis, management, and current challenges. *Cureus*. 2021;13(9):e17969. doi:10.7759/cureus.17969

55. Popescu A, Kao AH. Neuropsychiatric systemic lupus erythematosus. *Curr Neuropharmacol*. 2011;9(3):449–457. doi:10.2174/157015911796557984

56. Memon W, Aijaz Z, Afzal MS, Faryad S. Primary psychiatric disorder masking the diagnosis of lupus cerebritis. *Cureus*. 2020;12(11):e11643. doi:10.7759/cureus.11643

57. Magro-Checa C, Zirkzee EJ, Huizinga TW, Steup-Beekman GM. Management of neuropsychiatric systemic lupus erythematosus: current approaches and future perspectives. *Drugs*. 2016;76(4):459–483. doi:10.1007/s40265-015-0534-3

58. Cognitive Behavioral Therapy. InformedHealth.org. Institute for Quality and Efficiency in Health Care (IQWiG). August 7, 2013. Updated September 8, 2016. Accessed July 19, 2022. https://www.ncbi.nlm.nih.gov/books/NBK279297/

59. Rodríguez Huerta MD, Trujillo-Martín MM, Rúa-Figueroa Í, et al; Spanish SLE CPG Development Group. Healthy lifestyle habits for patients with systemic lupus erythematosus: a systemic review. *Semin Arthritis Rheum*. 2016;45(4):463–470. doi:10.1016/j.semarthrit.2015.09.003

60. Bordoni B, Escher AR Jr. Osteopathic principles: the inspiration of every science is its change. *Cureus*. 2021;13(1):e12478. doi:10.7759/cureus.12478

61. Solhjoo M, Bansal P, Goyal A, Chauhan K. Drug-induced lupus erythematosus. In: StatPearls. *StatPearls Publishing*; 2022. Accessed December 19, 2022. https://www.ncbi.nlm.nih.gov/books/NBK441889/

62. He Y, Sawalha AH. Drug-induced lupus erythematosus: an update on drugs and mechanisms. *Curr Opin Rheumatol*. 2018;30(5):490–497. doi:10.1097/BOR.0000000000000522

63. Clowse MEB, Magder LS, Witter F, Petri M. The impact of increased lupus activity on obstetric outcomes. *Arthritis Rheum*. 2005;52(2):514–521. doi:10.1002/art.20864

64. Kwok LW, Tam LS, Zhu T, Leung YY, Li E. Predictors of maternal and fetal outcomes in pregnancies of patients with systemic lupus erythematosus. *Lupus*. 2011;20(8):829–836. doi:10.1177/0961203310397967

65. Lateef A, Petri M. Managing lupus patients during pregnancy. *Best Pract Res Clin Rheumatol*. 2013;27(3):435–447. doi:10.1016/j.berh.2013.07.005

66. Abarientos C, Sperber K, Shapiro DL, Aronow WS, Chao CP, Ash JY. Hydroxychloroquine in systemic lupus erythematosus and rheumatoid arthritis and its safety in pregnancy. *Expert Opin Drug Saf*. 2011;10(5):705–714. doi:10.1517/14740338.2011.566555

67. Petri M. Pregnancy and systemic lupus erythematosus. *Best Pract Res Clin Obstet Gynaecol*. 2020;64:24–30. doi:10.1016/j.bpobgyn.2019.09.002

68. Yang H, Liu H, Xu D, et al. Pregnancy-related systemic lupus erythematosus: clinical features, outcome and risk factors of disease flares—a case control study. *PLoS One*. 2014;9(8):e104375. doi:10.1371/journal.pone.0104375

69. Andreoli L, Bertsias GK, Agmon-Levin N, et al. EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome. *Ann Rheum Dis*. 2017;76(3):476–485. doi:10.1136/annrheumdis-2016-209770

70. Brucato A, Cimaz R, Caporali R, Ramoni V, Buyon J. Pregnancy outcomes in patients with autoimmune diseases and anti-Ro/SSA antibodies. *Clin Rev Allergy Immunol*. 2011;40(1):27–41. doi:10.1007/s12016-009-8190-6

71. Hon KL, Leung AKC. Neonatal lupus erythematosus. *Autoimmune Dis*. 2012;2012:301274. doi:10.1155/2012/301274

72. Clowse MEB, Eudy AM, Kiernan E, et al. The prevention, screening and treatment of congenital heart block from neonatal lupus: a survey of provider practices. *Rheumatology*. 2018;57(suppl 5):v9–v17. doi:10.1093/rheumatology/key141

73. Mankee A, Petri M, Magder LS. Lupus anticoagulant, disease activity and low complement in the first trimester are predictive of pregnancy loss. *Lupus Sci Med*. 2015;2(1):e000095. doi:10.1136/lupus-2015-000095

74. Stagnaro-Green A, Akhter E, Yim C, Davies TF, Magder L, Petri M. Thyroid disease in pregnant women with systemic lupus erythematosus: increased preterm delivery. *Lupus*. 2011;20(7):690–699. doi:10.1177/0961203310394894

75. Keramiotou K, Anagnostou C, Kataxaki E, Galanos A, Sfikakis PP, Tektonidou MG. The impact of upper limb exercise on function, daily activities and quality of life in systemic lupus erythematosus: a pilot randomised controlled trial. *RMD Open*. 2020;6(1).e001141. doi:10.1136/rmdopen-2019-001141

76. Glück T, Müller-Ladner U. Vaccination in patients with chronic rheumatic or autoimmune diseases. *Clin Infect Dis*. 2008;46(9):1459–1465. doi:10.1086/587063

77. Rubin LG, Levin MJ, Ljungman P, et al.; Infectious Diseases Society of America. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis. 2014;58(3):309–318. doi:10.1093/cid/cit816

78. Altered immunocompetence. Centers for Disease Control and Protection. May 12, 2021. Accessed June 22, 2021. https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/immunocompetence.html

79. Ljungman P. Vaccination of immunocompromised patients. *Clin Microbiol Infect*. 2012;18(suppl 5):93–99. doi:10.1111/j.1469-0691.2012.03971.x

80. Salman-Monte TC, Torrente-Segarra V, Vega-Vidal AL, et al. Bone mineral density and vitamin D status in systemic lupus erythematosus (SLE): a systematic review. *Autoimmun Rev*. 2017;16(11):1155–1159. doi:10.1016/j.autrev.2017.09.011