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RHEUMATOLOGY ADVANCED PRACTICE PROVIDERS

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RHEUMATOLOGY ADVANCED PRACTICE PROVIDERS

Lupus

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Disclosures

Cassandra Dolecki, PharmD, MBA, BCACP, TTS

There are no relationships to disclose

Monica Richey, MSN, ANP-BC/GNP, BSN

Consultant: AstraZeneca, GSK

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Lupus: One Too Many Diseases

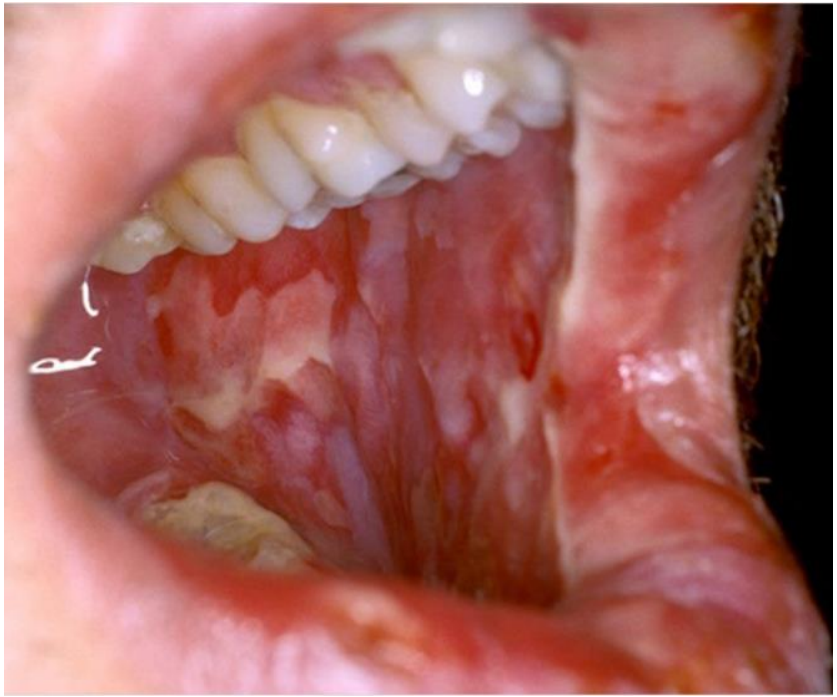
Monica Richey, MSN, ANP-BC/GNP, BSN

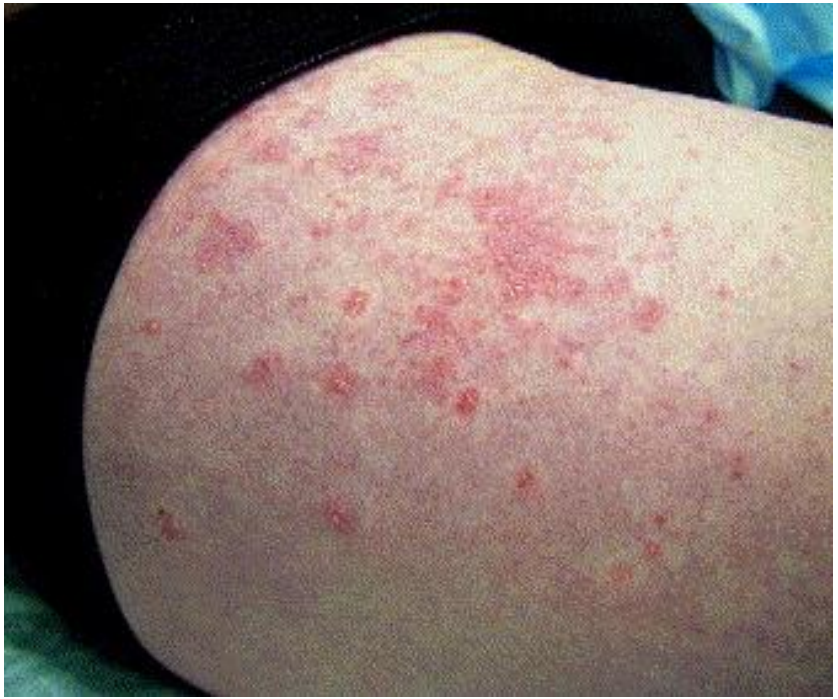
Case Presentation

- 63-year-old female presenting with severe fatigue, joint pain and positive ANA
- PMH of Hypertension, Hypothyroidism, knee osteoarthritis
- Labs with low titer Ds-dna all other are negative
- Start plaquenil – patient disappears for 6 months

6 Months Later

- Papular red macular rash in V shape over chest, back and shoulders
- Mucositis – severe
- Fevers
- Muscle weakness





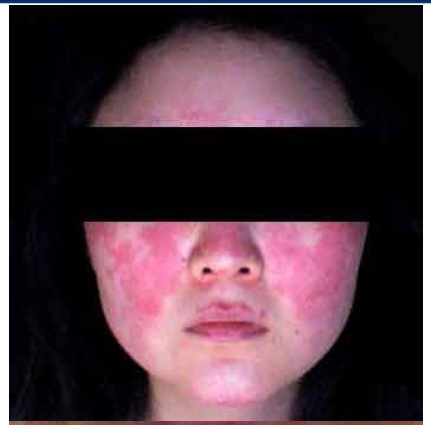
Results

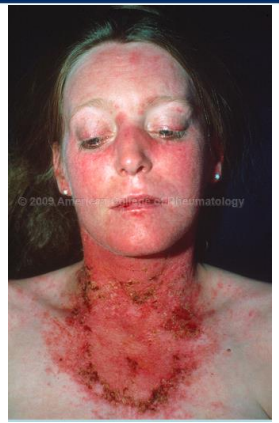
Positive	Other	Biopsy
ANA 1:1280 Speckled	Myoglobin 98	Telangiectasia sparse perivascular infiltrate of lymphocytes, weak granular IgG/IgM
SM/RNP	CPK 176	
DSDNA (318)	AST 344	
C3 49/C4 (8)	ALT 168	
Histone 4	WBC 2.43	
Coxsackie A/B - EB	Neut 1.37	
U2 snRNP		

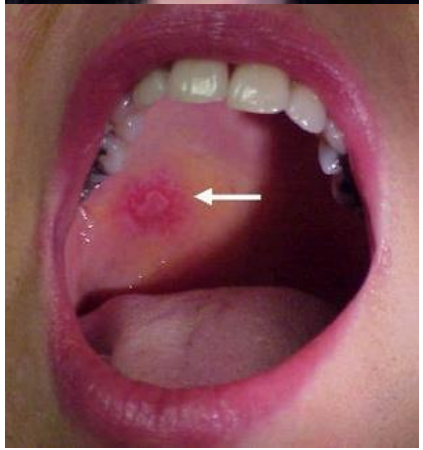
How Diseases in 1?

- **Neonatal Lupus**: Mother with anti-Ro/La, transient rash (1%) or congenital heart block (2%)
- **Drug-Induced Lupus**: disappear 3 months after stopping offending agent (maybe)
- **MCTD**: Raynaud's phenomenon, RNP and ACR criteria for scleroderma, RA, myositis – high prevalence of pulmonary hypertension and poorer prognosis.
- **Crossover and Overlap syndromes**: SLE + criteria for another RID, better prognosis.
- **Chronic Cutaneous Lupus**: (may also have SLE)
- **UCTD**: Lupus like symptoms without SLE criteria (ANA + Raynaud's) 1/3 complete resolution, 1/3 will evolve into RA/SLE
- **APS:** 1/3 of SLE have APA, 1/3 will have thromboembolic events

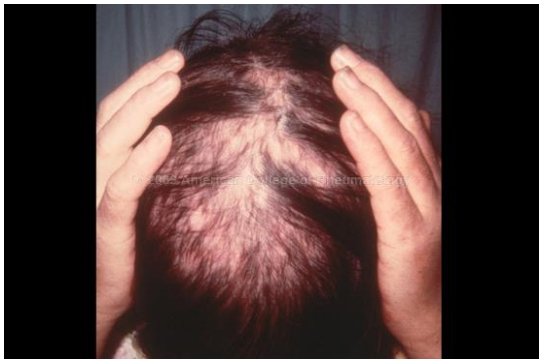
Cutaneous Manifestations

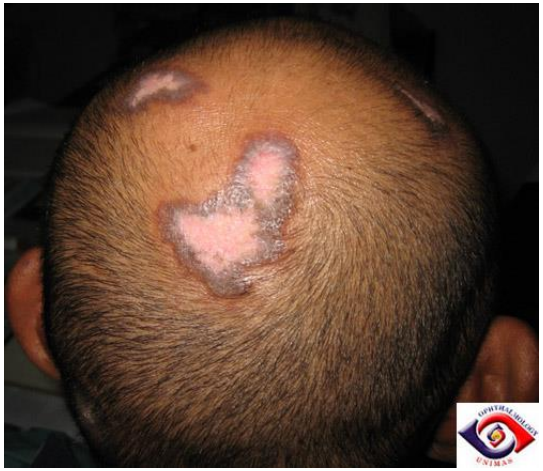


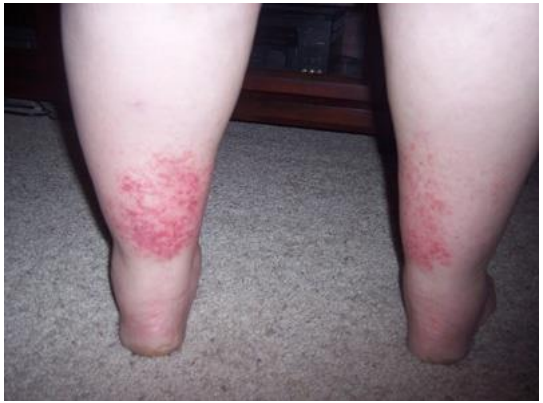


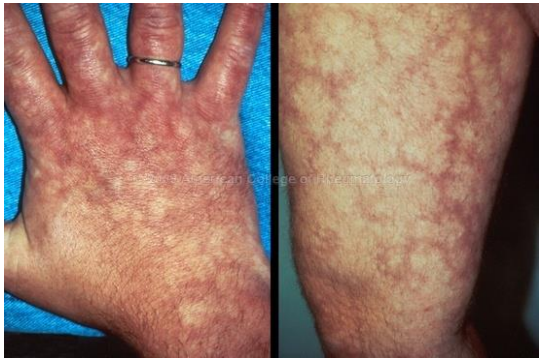


Cutaneous Manifestations

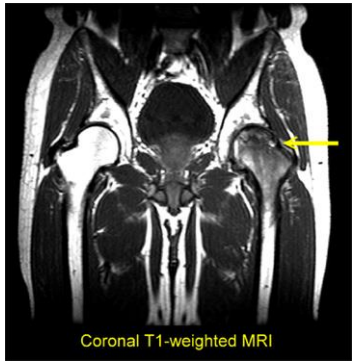


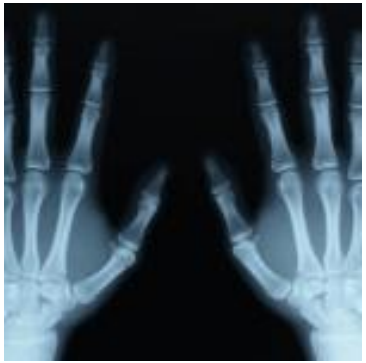


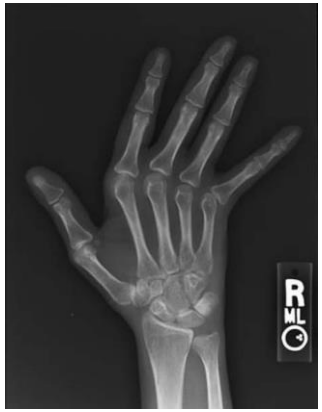




Musculoskeletal Manifestation

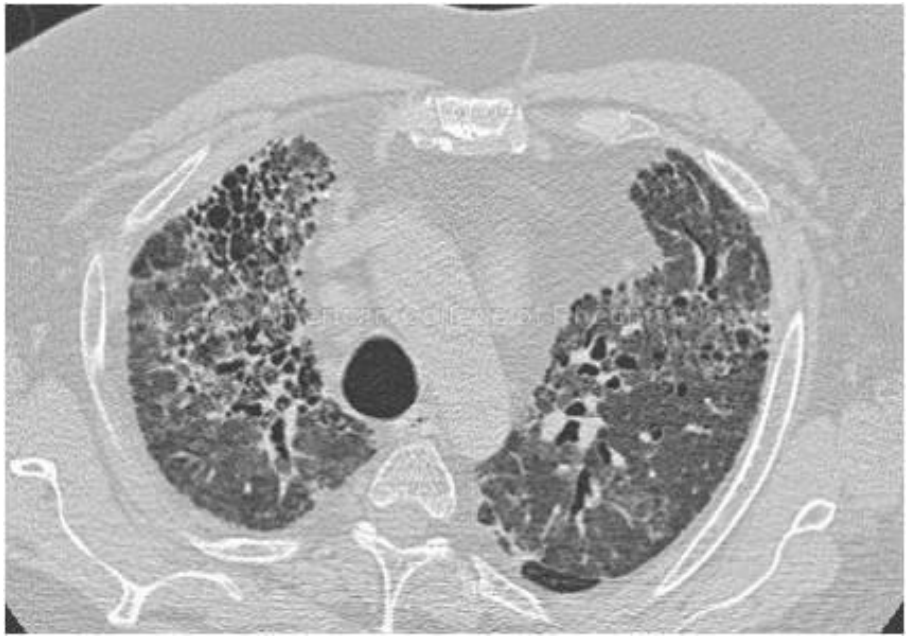


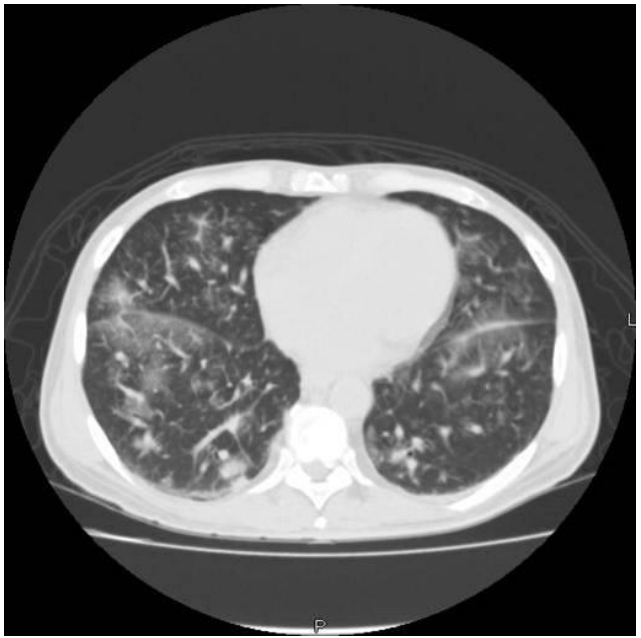




ACR image bank.

Pulmonary





Cardiovascular Manifestation

- Pericarditis: 60%, asymptomatic 25%
- Myocarditis and Myocardial dysfunction
- Hypertension: 25-30% of SLE patients
- Valvular Heart Disease: cellular debris, proliferative cells and immune complex vegetations (**Libman-Sacks endocarditis**); Apl, LT steroids, travel, infection. Tricuspid regurgitation= PAH; MVP common in SLE
- Accelerated Atherogenesis: CAD, Insulin resistance, metabolic syndrome, hyperlipidemia, pro-inflammatory HDL, steroids, obesity

New Classification Criteria 2019

Entry criterion

Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

↓

If absent, do not classify as SLE
If present, apply additive criteria

↓

Additive criteria

Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least one occasion is sufficient.
SLE classification requires at least one clinical criterion and ≥10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total score§.

Clinical domains and criteria	Weight
Constitutional	
Fever	2
Hematologic	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Neuropsychiatric	
Delirium	2
Psychosis	3
Seizure	5
Mucocutaneous	
Non-scarring alopecia	2
Oral ulcers	2
Subacute cutaneous OR discoid lupus	4
Acute cutaneous lupus	6
Serosal	
Pleural or pericardial effusion	5
Acute pericarditis	6
Musculoskeletal	
Joint involvement	6
Renal	
Proteinuria >0.5g/24h	4
Renal biopsy Class II or V lupus nephritis	8
Renal biopsy Class III or IV lupus nephritis	10

Immunology domains and criteria	Weight
Antiphospholipid antibodies	
Anti-cardiolipin antibodies OR	
Anti-β2GP1 antibodies OR	
Lupus anticoagulant	2
Complement proteins	
Low C3 OR low C4	3
Low C3 AND low C4	4
SLE-specific antibodies	
Anti-dsDNA antibody* OR	
Anti-Smith antibody	6

Total score:

↓

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

Is It Lupus ?

- Does it fulfill criteria?
- How would you treat?
- What else would you do?

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Lupus: Drug Updates

Cassandra Dolecki, PharmD, MBA, BCACP, TTS

Belimumab Expanded Indication

- December 2020: FDA approval for adults with active lupus nephritis who are receiving standard therapy.
- BLISS-LN trial: Phase 3 randomized, double-blind trial in adults with biopsy-proven, active LN
- Compared belimumab 10mg/kg or placebo, in addition to standard therapy
- Primary endpoint at week 104 was primary efficacy renal response
- Secondary endpoints:
  - Complete renal response
  - Renal-related events or death

Furie R, Rovin BH, Houssiau F et al. Two-year, randomized, controlled trial of belimumab in lupus nephritis. *N Eng J Med*. 2020; 383: 1117-1128.

BLISS LN

- Included 448 patients, 224 in each group
- At week 104:
  - PERR: 43% in belimumab group vs 32% in placebo (OR 1.6, 95% CI 1.0 to 2.3; p=0.03)
  - CRR: 30% in belimumab group vs 20% in placebo (OR 1.7, 95% CI 1.1 to 2.7; p=0.02)
  - Renal-related events or death: 15.7% in belimumab group vs 22.8% in placebo (HR 0.51, 95% CI 0.34 to 0.77; p=0.001)
- No new safety concerns

Furie R, Rovin BH, Houssiau F et al. Two-year, randomized, controlled trial of belimumab in lupus nephritis. *N Eng J Med*. 2020; 383: 1117-1128.

Voclosporin (Lupkynis)

- January 2021: FDA Approved for treatment of adult patients with active LN in combination with background immuno-suppressive therapy.
- Oral calcineurin inhibitor; leads to inhibition of lymphocyte proliferation, T-cell cytokine production, and expression of T-cell activation surface antigens
- AURORA-1: Phase 3, randomized, double blind, placebo-controlled trial
- Compared oral voclosporin 23.7mg twice daily to placebo, while on background therapy of mycophenolate mofetil

Lupkynis (voclosporin) package insert. Victoria, BC: Aurinia Pharmaceuticals; 2021 Jan.

AURORA-1

- Primary endpoint at 52 weeks: Complete renal response
- Key secondary endpoints:
  - Time to UPCR of ≤ 0.5 mg/mg
  - Partial renal response at weeks 24 and 52
  - Complete renal response at 24 weeks
  - Proportion of patients experiencing a confirmed decrease from baseline in eGFR
  - Duration of UPCR of 0.5 mg/mg or less
  - Change in UPCR, serum creatinine, urine protein, and eGFR from baseline at each timepoint;
  - Change from baseline in immunology parameters at weeks 24 and 52
  - Change from baseline in the SELENA-SLEDAI scores.
- 357 adults enrolled (179 in voclosporin group, 178 in placebo)

Rovin BH, Onno Teng YK, Ginzler EM et al. Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1): a double-blond, randomised, multicenter, placebo-controlled, phase 3 trial. *Lancet*. 2021; 397: 2070-2080.

AURORA-1

	Voclosporin group (n=179)	Placebo group (n=178)	OR or HR (95% CI)	p value
Primary endpoint*				
Complete renal response at 52 weeks	73 (41%)	40 (23%)	OR 6.65 (1.64-4.27)	<0.0001
Secondary endpoints				
Complete renal response at 24 weeks	58 (32%)	35 (20%)	OR 2.23 (1.34-3.72)	0.002
Partial renal response at 24 weeks	126 (70%)	89 (50%)	OR 2.43 (1.56-3.79)	< 0.001
Partial renal response at 52 weeks	125 (70%)	92 (52%)	OR 2.26 (1.45-3.51)	< 0.001
Time to UPCR ≤ 0.5 mg/mg, days	169 (141-214)	372 (295-NC)	HR 2.02 (1.51-2.70)	< 0.001
Time to 50% reduction in UPCR, days	29 (29-32)	63 (57-87)	HR 2.05 (1.62-2.60)	< 0.001

Rovin BH, Onno Teng YK, Ginzler EM et al. Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1): a double-blond, randomised, multicenter, placebo-controlled, phase 3 trial. *Lancet*. 2021; 397: 2070-2080.

Voclosporin

- Black Box Warning: Malignancies and Serious Infections
- Drug Interactions!
  - Contraindicated with concurrent use of strong CYP 3A4 inhibitors
- Warnings/Precautions: nephrotoxicity, hypertension, neurotoxicity, hyperkalemia, QTc prolongation
- Most common adverse reactions: decreased GFR, hypertension, diarrhea, headache, anemia, cough, upper respiratory tract infection
- Pregnancy: may cause fetal harm

Lupkynis (voclosporin) package insert. Victoria, BC: Aurinia Pharmaceuticals; 2021 Jan.

Anifrolumab-fnia (Saphnelo)

- August 2021: FDA approved for moderate to severe SLE who are receiving standard therapy
- Human IgG1κ monoclonal antibody that binds to subunit 1 of the type I interferon receptor (IFNAR1)
- Dosing: 300 mg IV every 4 weeks
- Two Phase 3 trials: TULIP-1 and TULIP-2
- Exclusion criteria: severe LN and severe CNS Lupus

Saphnelo (anifrolumab-fnia) package insert. Wilmington, DE: AstraZeneca; 2021 Aug.

TULIP-1

- Phase 3, randomized, double blind, placebo-controlled, parallel group trial
- Persons aged 18-70 with a diagnosis of moderate to severely active SLE (among other inclusion criteria)
- Anifrolumab 300 mg, anifrolumab 150 mg, or placebo, every 4 weeks for 48 weeks
- Primary outcome: proportion of patients who achieved an SRI-4 at week 52 in the anifrolumab 300 mg group vs placebo group
- Key secondary outcomes for anifrolumab 300 mg vs placebo included:
  - The proportion of patients in interferon test-high subgroup who achieved SRI-4 responses at week 52
  - Proportion of patients on 10 mg/day or more of corticosteroids at baseline who achieved a sustained dose reduction to ≤ 7.5mg/day from week 40 to 52
  - Proportion of patients with a CLASI activity score of ≥ 10 at baseline who achieved ≥ 50% reduction in CLASI score by week 12
  - Proportion of patients who achieved SRI-4 responses at week 24
  - Annualized flare rate through week 52

Furie RA, Morand EF, Bruce IN, et al. Type I interferon inhibitor anifrolumab in active systemic lupus erythematosus (TULIP-1): a randomised, controlled, phase 3 trial. *Lancet*. 2019;1:e208-2019.

TULIP-1

- The primary endpoint of achieving SRI-4 at week 52 was achieved by 36% in the anifrolumab 300 mg group and 40% in the placebo group (p=0.41).
- Secondary endpoints:
  - In the high interferon gene signature test subgroup, SRI-4 responses at week 52 were similar in those that received anifrolumab (36%) and placebo (39%), difference -3.4 [95% CI 14.4 to 7.6; nominal p=0.549].
  - Among patients receiving prednisone or equivalent of at least 10mg per day, a numerically greater portion of the anifrolumab 300 mg (42 of 103, 41%) than the placebo group (33 of 102, 32%) achieved a dose reduction to the target of 7.5 mg per day or less, sustained from week 40 to week 52 (difference 8.9 [95% CI -4.1 to 21.9]).
  - Among patients with CLASI scores of ≥ 10 at baseline, a reduction of at least 50% from baseline by week 12 was achieved by 42% of patients in the anifrolumab group vs 25% in the placebo group (difference 17.0 [95% CI -0.3 to 34.3]).
  - SRI-4 rates at 24 weeks were similar to week 52; 42% in the anifrolumab 300 mg group vs 41% in the placebo group (difference 0.6 [95% CI -9.4 to 10.6], nominal p-value 0.905).
  - The annualized flare rate was numerically lower in the anifrolumab group (0.6) compared to the placebo group (0.72; rate ratio 0.83 [95% CI 0.6 to 1.14]).
  - BICLA response at week 52 was achieved in 37% in the anifrolumab 300 mg group compared to 27% in the placebo group (difference 10.1 [95% CI 0.6 to 19.7]).

Furie RA, Morand EF, Bruce IN, et al. Type I interferon inhibitor anifrolumab in active systemic lupus erythematosus (TULIP-1): a randomised, controlled, phase 3 trial. *Lancet*. 2019;1:e208-2019.

TULIP-2

- Phase 3, randomized, double blind, placebo-controlled, parallel group trial
- Persons aged 18-70 with a diagnosis of moderate to severely active SLE (among other inclusion criteria)
- Anifrolumab 300 mg or placebo, IV every 4 weeks for 48 weeks
- Primary outcome: was the difference between the two groups in the percentage of patients who had a BICLA response at week 52

Morand EF, Furie R, Tanaka Y, et al. Trial of anifrolumab in active systemic lupus erythematosus. *N Eng J Med*. 2020; 382: 211-221.

TULIP-2

- Key Secondary Outcomes:
  - A BICLA response at 52 weeks in patients with a high interferon gene signature at baseline
  - A reduction in the glucocorticoid dose to ≤ 7.5 mg per day, sustained from week 40 to week 52, among patients with a baseline dose of ≥ 10 mg/day
  - A reduction of ≥ 50% in the CLASI score (Cutaneous Lupus Erythematosus Disease Area and Severity Index) at week 12 among patients with moderate to severe cutaneous activity (CLASI ≥ 10)
  - A reduction of ≥ 50% from baseline in counts of both swollen joints and tender joints at week 52 among patients with ≥ 6 swollen joints and ≥ 6 tender joints at baseline
  - Annualized flare rate through week 52

Morand EF, Furie R, Tanaka Y, et al. Trial of anifrolumab in active systemic lupus erythematosus. *N Eng J Med*. 2020; 382: 211-221.

TULIP-2

- The primary endpoint of BICLA response at week 52 occurred in 47.8% of patients receiving anifrolumab and 31.5% of patients receiving placebo (p=0.001).
  - In the subpopulation of a high interferon gene signature, the percentage of patients with a BICLA response at week 52 was 48.0% in the anifrolumab group and 30.7% in the placebo group (p=0.002).
  - In those with a low interferon gene signature, the percentage of patients with a BICLA response was 46.7% in the anifrolumab group and 35.5% in the placebo group.
- Among patients receiving ≥ 10 mg daily of prednisone, a sustained reduction in prednisone to ≤ 7.5 mg/day was achieved in 51.5% of anifrolumab patients vs. 30.2% of patients receiving placebo (p=0.01).
- Among patients with at least moderate skin involvement (CLASI ≥ 10), a reduction of ≥ 50% in the CLASI at week 12 occurred in 49.0% of patients in the anifrolumab group vs to 25.0% of patients in the placebo group (p=0.04).
- Among patients with ≥ 6 swollen joints and ≥ 6 tender joints at baseline, a reduction of ≥ 50% in number of both swollen and tender joints was achieved in 42.2% of patients in the anifrolumab group vs. to 37.5% in the placebo group. This difference was not statistically significant (p=0.55).
- The annualized flare rate amongst patients in the anifrolumab group was 0.43 compared to 0.64 in the placebo group, although this was not statically significant (p=0.08).

Morand EF, Furie R, Tanaka Y, et al. Trial of anifrolumab in active systemic lupus erythematosus. *N Eng J Med*. 2020; 382: 211-221.

Adverse Reactions

	Anifrolumab-fnia (n=459)	Placebo (n=466)
Upper respiratory tract infections	34	23
Bronchitis	11	5.2
Infusion reactions	9.4	7.1
Herpes zoster	6.1	1.3
Cough	5.0	3.2
Respiratory tract infections	3.3	1.5
Hypersensitivity	2.8	0.6

Saphnelo (anifrolumab-fnia) package insert. Wilmington, DE: AstraZeneca; 2021 Aug.

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Thank you