CONTROVERSIES IN MANAGEMENT AND TREATMENT OF CUTANEOUS LUPUS PATIENTS
CONFLICTS OF INTEREST

DISCLOSURE OF RELATIONSHIPS WITH INDUSTRY

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U090 – Controversies in Management and Treatment of Cutaneous Lupus and Dermatomyositis Patients

DISCLOSURES

Biogen Inc.: Investigator – Grants
Daavlin Inc.: Investigator – Grants
Pfizer: Investigator
OUTLINE

- Treatment/Management of Cutaneous Lupus and Patients
- Management and Treatment “Controversies”
TREATMENT AND MANAGEMENT OF CUTANEOUS LUPUS
CUTANEOUS LUPUS AT UNIVERSITY OF TEXAS SOUTHWESTERN

- Subacute Cutaneous Lupus Erythematous
  - Case series of 27 patients
  - Associated with anti-Ro antibody
- Classification of Cutaneous Lupus Erythematosus
  - Acute
  - Subacute
  - Chronic

1Sontheimer RD et al, Arch Dermatol 1979; 115:1409-15
MY WORKUP ON CUTANEOUS LUPUS PATIENTS

New CLE diagnosis

Review of systems
Physical examination
Medical chart review

Laboratory Testing:
- CBC with differential
- ANA
- Urinalysis
Consider:
- ENA panel
- Anti-dsDNA antibody
- ESR/CRP
- C3 and C4 complements

ANA positive

Further Laboratory Testing:
- ENA panel
- Anti-dsDNA antibody
- ESR/CRP
- C3 and C4 complements

Meets criteria for SLE
Refer to rheumatology and other specialists as indicated by disease manifestations

CLE without SLE
Start first-line therapy

ANA negative

Start first-line therapy
If unstable, patients should be followed on biweekly to monthly basis.

If stable, check every 3-6 months.

Taper medications during fall/winter.
TREATMENT LADDER FOR CUTANEOUS LUPUS

Limited
- Photoprotective methods
- Topical Steroids/Immunomodulators
- Intraleisional Steroids (2.5-10 mg/cc)

Modest/Refractory Limited
- Prednisone (up to 0.5 mg/kg/day) for rapid symptom reduction
- Hydroxychloroquine (200 mg QD-BID) (based on weight)
- Quinacrine (100 mg QD)
- Chloroquine (125-250 mg QD) (based on weight)

Diffuse/Refractory Modest

• Prednisone (up to 1 mg/kg/day)
• Mycophenolate mofetil (1000-1500 mg BID)
• Methotrexate (7.5-25 mg QWK)
• Azathioprine (2-3 mg/kg/day)
• Cyclophosphamide (500-750 mg/m²/mo)
• Cyclosporine (2-5 mg/kg/day)
• Thalidomide (25-100 mg qHS), lenalidomide (2.5-10 mg qHS)
• Retinoids (e.g. acitretin (10-50 mg QD), isotretinoin (0.5-1 mg/kg/day)
• Dapsone (25-100 mg BID)
• Intravenous immunoglobulin (2 mg/kg/mo)

MANAGEMENT AND TREATMENT “CONTROVERSIES”
How do you monitor CLE-only patients for progression to SLE?
- Who is at risk?
- What is their prognosis?

How do you dose hydroxychloroquine?

Anything new for treatments for CLE?
52 y.o. AA female with history of DLE lesions on scalp, face, ears, arms and legs

Current medications – clobetasol 0.05% ointment

ACR SLE criteria – DLE, photosensitivity

Labs – ANA negative, CBC WNL, C3, C4 WNL, Cr WNL, U/A negative for protein

Hydroxychloroquine 300 mg QD started
CASE #1

- Patient lost to follow-up
- Returns 10 month later, still on hydroxychloroquine
- New complaints of oral ulcers, skin lesions on face, diffuse arthralgias, muscle pains
WHAT WOULD YOU DO NEXT?

A) Repeat ANA
B) Order complete blood count
C) Order urinalysis
D) A+B
E) All of the above
CASE #1

- Labs
  - ANA – 1:320 speckled
  - CBC, U/A, CMP normal
  - Negative dsDNA Ab
  - ENA panel – RNP Ab positive at >8
  - C3, C4 - normal

- Refer to rheumatology
  - ACR SLE criteria - +DLE, photosensitivity, oral ulcers, +ANA

- Mycophenolate mofetil offered but patient declined
CUTANEOUS LUPUS PATIENTS CAN PROGRESS TO SLE

- 156 cutaneous patients in Mayo Clinic
  - 13% developed SLE.
  - Mean time: 8.2 years
  - Cumulative incidence of SLE: 5% at 5 years, 23% at 25 years

CUTANEOUS LUPUS PATIENTS CAN PROGRESS TO SLE

- Population-based cohort study of 1088 cutaneous lupus patients in Sweden
  - 18.1% of patients were later diagnosed with SLE
  - 12.1% risk (at year 1) -> 18.1% risk (at year 3)
  - Females at higher risk than males
  - DLE - 16.7% risk of developing SLE in 3 years
  - SCLE - 24.7% risk of developing SLE in 3 years

Gronhagen CM, et al, Br J Dermatol 2011; 1335-1341
Most cutaneous lupus patients progressing to SLE have mild systemic disease.

- 77 cutaneous lupus patients
- 13 (16.9%) progressed to SLE
  - Risk factors – positive ANA titer, generalized DLE, higher # of SLE criteria
  - SLE criteria mostly mucocutaneous
  - Severity of disease mostly remains mild
- UTSW – 10/66 (15.2%) developed SLE

| Table 2. Criteria Met by Patients Who Transitioned to SLE |
|---------------------------------|--------------|
| Criteria                        | SLE<sub>c</sub>, No. (%) (n = 13) |
| Photosensitivity                | 12 (92)      |
| ANA                             | 9 (69)       |
| Discoid rash<sup>a</sup>        | 8 (62)       |
| Oral ulcers                     | 7 (54)       |
| Arthritis                       | 6 (46)       |
| Malar rash<sup>a</sup>          | 4 (31)       |
| Hematologic                     | 4 (31)       |
| Antibodies                      | 3 (23)       |
| Renal                           | 2 (15)       |
| Pleuritis                       | 0            |
| Neurologic                      | 0            |
| Mucocutaneous criteria only<sup>b</sup> | 1 (8)     |
| Mucocutaneous criteria and antibodies<sup>c</sup> | 3 (23) |

Chong, BF, JAMA Dermatol 2014; 150:296
CHILDREN WITH DISCOID LUPUS CAN DEVELOP SLE

- Retrospective review of 40 DLE pediatric patients
  - 6 with concurrent SLE
  - 9 (26%) later diagnosed with SLE
    - All progressed within 3 years
    - Average age at progression – 11 years
  - 89% had just mucocutaneous-limited disease and abnormal laboratory tests

CLINICAL SIGNS AS PREDICTORS OF SLE DEVELOPMENT

- Generalized DLE
- Periungual telangiectasias
- Arthritis/arthralgias
- Laboratory abnormalities
  - Leukopenia
  - Positive ANA

RECOMMENDATIONS FOR FOLLOW-UP

QUESTIONS

- How do you monitor CLE-only patients for progression to SLE?
  - Who is at risk?
  - What is their prognosis?
- How do you dose hydroxychloroquine?
- Anything new for treatments for CLE?
CLE RESPONSE RATE TO ANTIMALARIALS IS OVER 60%

- Meta-analysis of 31 studies (1990 courses of treatment)
- Overall response rate to antimalarials in CLE patients – 63%
- Response rate highest in acute CLE (91%) and lowest in Chilblain’s lupus (31%).

Chasset F et al, Br J Dermatol 2017; 177:14-15
HYDROXYCHLOROQUINE IS THE FIRST-LINE ANTI-MALARIAL FOR CUTANEOUS LUPUS

- Requires at least 2-3 months to take effect
- Side effects: GI upset, skin pigmentation, retinal toxicity
- Rare side effects: cardiotoxicity, myopathy, agranulocytosis
Retinopathy presents as initially premaculopathy
Progression results in bull’s-eye maculopathy (paracentral scotomas)
2011 AAO (Ophthalmology) screening recommendations for hydroxychloroquine
- Baseline examination within 1st year of use
- Annual screening after 5 years
- Higher risk patients (history of retinal disease, renal, or liver disease, short stature, obesity)

Marmor MF et al, Ophthalmology 2011; 118:415-422
A LOWER MAXIMUM DOSE OF HYDROXYCHLOROQUINE IS RECOMMENDED

- Retrospective study of 2361 patients on hydroxychloroquine for at least 5 years
  - Prevalence of retinopathy – 7.5%
  - 4-5 mg/kg/day - <2% had retinopathy within 1st 10 years, increased to ~20% in next 10 years.
  - >5 mg/kg/day - ~10% risk of retinal toxicity within 10 years, almost 40% risk in next 10 years

Melles RB, Marmor MF. JAMA Ophthalmol 2014; 132:1453-60
<table>
<thead>
<tr>
<th>Drug</th>
<th>2011 Dosing Guidelines</th>
<th>2016 Dosing Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxychloroquine (Plaquenil)</td>
<td>&lt;6.5 mg/kg/day (ideal body weight)</td>
<td>&lt;5 mg/kg/day (actual body weight)</td>
</tr>
</tbody>
</table>

Do we adhere to this dosing guideline at all times?
58 y.o. AA female with history of SLE presenting with complaints of tender lesions on R leg for one month.

Medications – hydroxychloroquine 200 mg BID, clobetasol ointment

SLE history – +malar rash, discoid rash, photosensitivity, oral ulcers, hematologic disorder (lymphopenia, leukopenia), +ANA (1:640), +Sm Ab, +dsDNA Ab, hypocomplementemia
Differential Diagnosis

- Lupus panniculitis/lupus profundus
- Discoid lupus erythematosus
- Erythema induratum
- Atypical erythema nodosum
- Tumid lupus
CASE #2

- Skin biopsy – consistent with tumid lupus erythematosus
- Patient states that she does not want to be on more potent immunosuppressant medications
- Only antimalarial option - hydroxychloroquine
- Plan – increase hydroxychloroquine to 600 mg daily
  - Patient is 70 kg
  - Patient has been on hydroxychloroquine for 1.5 years
BLOOD LEVELS OF HYDROXYCHLOROQUINE CORRELATE WITH TREATMENT RESPONSE IN CLE PATIENTS

- 300 CLE patients treated with hydroxychloroquine for ≥ 3 months\(^1\)
  - Complete remission associated with higher drug levels
- 34 patients treated with higher doses of hydroxychloroquine (blood level > 750 ng/mL)\(^2\)
  - 81% showed treatment response
  - 11/18 had flares with drug taper.
  - Recommend in patients with cumulative drug doses of < 1000 g.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Drug levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete remission</td>
<td>910 ng/mL</td>
</tr>
<tr>
<td>Partial remission</td>
<td>692 ng/mL</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>569 ng/mL</td>
</tr>
</tbody>
</table>

\(^1\)Frances C, et al, Arch Dermatol 2012; 148:479-84
TAKEAWAY

- Consider higher doses of hydroxychloroquine for a short period in the following patients
  - Those who are flaring
  - CLE subtypes with higher likelihood of treatment response (ACLE, tumid lupus)
  - Low risk of retinal toxicity
    - Cumulative dose <1000 g
    - No history of liver, kidney disease
    - No history of retinal disease
  - Ask patient’s ophthalmologist if you are not sure
How do you monitor CLE-only patients for progression to SLE?
- Who is at risk?
- What is their prognosis?

How do you dose hydroxychloroquine?

Anything new for treatments for CLE?
54 y.o. AA female with history of HTN, DM II, SLE and refractory DLE

Chief complaints – burning, pain, insomnia

SLE criteria - +DLE, photosensitivity, arthritis, lupus nephritis, +ANA, serositis

Current SLE medications:
- Belimumab 10 mg/kg IV
- Prednisone 10 mg QD
- Mycophenolate mofetil 1500 mg BID
- Chloroquine 250 mg QD, quinacrine 50 mg QD
**WHAT ARE OTHER TREATMENTS?**

**Diffuse/Refractory Modest**

- Prednisone (up to 1 mg/kg/day)
- Mycophenolate mofetil (1000-1500 mg BID)
- Methotrexate (7.5-25 mg QWK)
- Azathioprine (2-3 mg/kg/day)
- Cyclophosphamide (500-750 mg/m²/mo)
- Cyclosporine (2-5 mg/kg/day)
  - Thalidomide (25-100 mg qHS), lenalidomide (2.5-10 mg qHS)
  - Retinoids (e.g. acitretin (10-50 mg QD), isotretinoin (0.5-1 mg/kg/day)
  - Dapsone (25-100 mg BID)
  - Intravenous immunoglobulin (2 mg/kg/mo)

CASE #3

- Started on lenalidomide 2.5 mg QHS, titrated up to 5 mg QHS
  - Quinacrine, belimumab d/c’d
- Reported improvement in pain, redness
- D/C’d due to leukopenia, thrombocytopenia
Lenalidomide – thalidomide analog

Open-label trial of 5 refractory CLE patients
- 5 mg QD x 6 weeks
- 10 mg QD in non-responders, 5 mg QOD in responders

CLASI activity scores improved from 21.4 (baseline) to 8.6 (week 12)

Okon L et al, J Am Acad Dermatol 2014; 70:583-4
LENALIDOMIDE FOR TREATMENT OF CUTANEOUS LUPUS

- 16 patients with DLE and SCLE\(^1\)
  - Median R-CLASI activity decreased from 23 to 4 (p<0.001)
  - Side effects – weakness, insomnia, headache
- 8 patients with CLE\(^2\)
  - 5/8 achieved complete response
  - 4 patients with mild abnormal CBCs

LENALIDOMIDE REQUIRES CLOSE MONITORING OF ADVERSE EFFECTS

- **Doses** – 2.5 mg to 10 mg/day
- **Adverse effects** – neutropenia, thrombocytopenia, leukopenia, increased risk of DVT/PE, nausea, diarrhea, constipation, fatigue, headache
  - **Teratogenicity** – Revlimid REMS program used to mitigate risk
  - **Less risk of peripheral neuropathy than thalidomide**
LENALIDOMIDE REQUIRES CLOSE MONITORING OF ADVERSE EFFECTS

- Weekly CBC with differential x 4-8 weeks, then once a months
- Females of childbearing potential - two forms of contraception
SIFALIMUMAB MAY BE EFFECTIVE FOR CLE

- Sifalimumab – anti-interferon-α mAb
- Phase IIb RCT in 431 SLE patients treated with IV sifalimumab 200 mg, 600 mg, or 1200 mg or placebo q4 weeks
  - More CLE patients on 200 mg and 1200 mg doses reached treatment response than placebo at week 52
- Adverse events – SLE flares, infections

Anifrolumab – type I IFN receptor antagonist

Phase IIIB of 305 SLE patients treated with IV anifrolumab 300 mg, 1000 mg or placebo q4 weeks

- More anifrolumab-treated patients with CLE (63% (300 mg), 58.3% (1000 mg)) showed treatment response than placebo (30.8%)
- Adverse effects – headache, infections

Furie R et al, Arthritis Rheum 2017; 69:376-386
PHASE I TRIAL FOR IFN-GAMMA ANTIBODY IN DLE SHOWS NO CLINICAL DIFFERENCE

- **AMG 811** – anti-IFN-γ antibody
- Phase I double-blind RCT cross-over study
- 180 mg SQ or placebo
- 16 patients with DLE
- No significant changes in CLASI-A score
- 14/15 patients experienced minor AEs

Screen for SLE in all patients with complete H+P and lab testing.

Consider increasing hydroxychloroquine to higher doses temporarily in patients who are flaring and have high likelihood of response.

New treatments including lenalidomide and anti-interferon monoclonal antibodies look promising for CLE.
REFERENCES

- Chasset F et al, Br J Dermatol 2017; 177:14-15
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- Marmor MF et al, Ophthalmology 2011; 118:415-422
- Melles RB, Marmor MF. JAMA Ophthalmol 2014; 132:1453-60
- Okon L et al, J Am Acad Dermatol 2014; 70:583-4
- Sontheimer RD et al, Arch Dermatol 1979; 115:1409-15
The Dermatology Foundation has supported & advanced my career.