Guidelines: Systemic Therapies

Mark Lebwohl, MD
Sol and Clara Kest Professor
And Chairman
Department of Dermatology
The Mount Sinai School of Medicine
Mark Lebwohl is an employee of Mount Sinai which receives research funds from: Abbvie, Amgen, Boehringer Ingelheim, Celgene, Eli Lilly, Janssen / Johnson & Johnson, Kadmon, Medimmune/Astra Zeneca, Novartis, Pfizer, Valeant and ViDac.

Dr. Lebwohl is also a consultant for Allergan, Aqua Leo-pharma, and Promius.
1. A 53 y.o. female with psoriasis on 40% BSA has a history of uncontrolled hypertension. Her serum creatinine is 3.2 and her serum cholesterol is 280 with an unfavorable HDL/LDL ratio and triglycerides of 283. The patient has failed monotherapy with UVB and with PUVA. She cannot afford treatment with any of the biologics. Which of the following treatments would most likely produce the best effect?

answers on the next slide
a. Cyclosporine
b. Methotrexate
c. Acitretin
d. Apremilast
e. c or d
2. A 24 y.o. obese male with psoriasis on 50% BSA plans to start methotrexate. He does not drink alcohol and is otherwise in good health. When should he undergo liver biopsy?
1. Liver biopsy is no longer routinely required in this patient according to the new guidelines.

2. The pros and cons of liver biopsy should be discussed with this patient and he should make an informed decision.

3. The patient should undergo liver biopsy 2-6 months after starting mtx and again after 1-1.5g of mtx.

4. The patient's first liver biopsy should take place after 1-1.5g of mtx.

5. Mtx is contraindicated in this patient.
Guidelines of care for the management and treatment of psoriasis with traditional systemic agents.
36 y.o. WM
Plaque psoriasis, 70%
Topical Rx – failed
UVB and PUVA – failed
Mtx 15 mg/w
Bactrim DS bid for UTI
Check bloods 2 days after Mtx
• 1972 FDA approval for psoriasis, 1st guidelines published: BL liver bx & routine liver bx’s with cumulative doses
• 1988 FDA approval for RA
• ACR guidelines do not call for routine liver bx
• 1998 guidelines removed need for pretreatment bx except in those with pre-existing liver disease; routine bx with cumulative doses
A 21-year Experience With Major Hemorrhage After Percutaneous Liver Biopsy


- 9,212 liver bx’s
- 10 fatal (0.11\%) and 22 nonfatal (0.24\%) hemorrhages
If we’re going to subject patients to the risks of liver bx, we should limit biopsies to those patients who are at most risk from MTX.

Can we accurately predict who’s going to develop hepatic fibrosis?
Role of non-alcoholic steatohepatitis in methotrexate-induced liver injury
Langman G, Hall PM, Todd G.

• 17/24 pts on longterm MTX→NASH
• 13/17: obese/d.m.; 4/17: mean 6.5g MTX
• 7/24: nl bx, mean 3.8g MTX
169 liver bx’s in 71 psoriasis pts on MTX

- Hepatic fibrosis: 71%
- In pts with risk fx: 96%
  - obesity 14/15
  - diabetes 7/7
  - ETOH 9/9
- ↑LFT’s not associated with fibrosis

Rosenberg P, et al
Methotrexate and psoriasis: 2009 National Psoriasis Foundation Consensus Conference.
Kalb RE, Strober B, Weinstein G, Lebwohl M.
Baseline Monitoring

- CBC + plts
- BUN/Creatinine
  (CCl [Cockroft Gault] when indicated)
- ALT, AST, Alk phos, Albumin, Bilirubin
- When indicated/Optional:
  - Hepatitis B & C serologies
  - HIV
  - Pregnancy test
  - PPD
Calculated glomerular filtration rate or creatinine clearance when indicated. The Cockroft and Gault formula can be used to estimate the creatinine clearance in adults:

FOR MEN: Estimated creatinine clearance

\[ = \frac{(140 - \text{Age [y]}) \times (\text{Body wt. [kg]})}{72 \times \text{Serum creatinine (mg. 100 ml-1)}} \]

FOR WOMEN: Estimated creatinine clearance

\[ = \text{MALE creatinine clearance} \times 0.85 \]
Continued Monitoring

• CBC + plts 7-14 d. p. ↑dose
  then q2-4 w. x few mos.
  then q 1-3 mos.
• BUN/Creatinine q 2-3 mos.
• ALT, AST, Alk phos, Albumin q4-12 w.
• When indicated:
  pregnancy
“In patients without risk factors for hepatic fibrosis, liver biopsies may not be indicated or the frequency markedly reduced.”

2009 NPF consensus statement
### Table III. Monitoring for hepatotoxicity in low risk patients

- No baseline liver biopsy
- Monitor liver function tests monthly for the first 6 months and then every 1-2 months thereafter
Table II.
Risk factors for hepatic toxicity from methotrexate

- History of or current excessive alcohol consumption
- Persistent abnormal liver chemistry studies
- History of liver disease including chronic hepatitis B or C
- Family history of inheritable liver disease
- Diabetes mellitus
- Obesity
- History of significant exposure to hepatotoxic drugs or chemicals
- Lack of folate supplementation
- Hyperlipidemia
Table IV. Monitoring for hepatotoxicity in high risk patients

- Consider the use of a different systemic agent
- Consider delayed baseline liver biopsy (after 2-6 months of therapy to establish medication’s efficacy and tolerability)
- Repeat liver biopsies after approximately 1 – 1.5 g of therapy
Fibrosis-4 (FIB-4) Calculator

The Fibrosis-4 score helps to estimate the amount of scarring in the liver. Enter the required values to calculate the FIB-4 value. It will appear in the oval on the far right (highlighted in yellow).

FIB-4 = \frac{\text{Age (years)} \times \text{AST Level (U/L)}}{\text{Platelet Count (10^9/L)} \times \sqrt{\text{ALT (U/L)}}}

Interpretation:
Using a lower cutoff value of 1.45, a FIB-4 score <1.45 had a negative predictive value of 90% for advanced fibrosis (Ishak fibrosis score 4-6 which includes early bridging fibrosis to cirrhosis). In contrast, a FIB-4 >3.25 would have a 97% specificity and a positive predictive value of 65% for advanced fibrosis. In the patient cohort in which this formula was first validated, at least 70% patients had values <1.45 or >3.25. Authors argued that these individuals could potentially have avoided liver biopsy with an overall accuracy of 86%.
Effect of folic or folinic acid supplementation on the toxicity and efficacy of methotrexate in rheumatoid arthritis.
Van Ede A, et al.

• Folate and folinic acid prevent ↑ LFT’s.
Treatment of gastrointestinal symptoms associated with methotrexate therapy for psoriasis.

Duhra P.

*J Am Acad Dermatol* 28:466-9; 1993

- Folate 5 mg/d. prevents methotrexate nausea
Pancytopenia secondary to methotrexate therapy in rheumatoid arthritis.


- 70 cases, 12 deaths
- 1.4% in prospective trials
- Risk fx: ↑BUN, Cr; ↓albumin; infection; medications; age
57-year-old
Psoriasis – 60% BSA
Cyclosporine clear

- K+ 5.8
- Mg#
- ↑BP
- Bilirubin 2.2
- Uric acid 7.2
- Cholesterol 308
- TG’s 563
Renal effects of amlodipine in normotensive renal transplant recipients.

Venkat Raman G, et al.  
*Nephrol Dial Transplant*  

• Amlodipine reduced creatinine
Amlodipine (Norvasc)

2.5, 5, and 10 mg

• start with 5mg/d.
• increase up to 10 mg/d.
Cyclosporine and psoriasis: 2008 National Psoriasis Foundation Consensus Conference.

Rosmarin DM, Lebwohl M, Elewski BE, Gottlieb AB.

CYCLOSPORINE SIDE EFFECTS

- Nephrotoxicity
- Hypertension
- Hypomagnesemia, Hyperkalemia
- Hyperlipidemia
- Drug interactions
- Hypertrichosis
- Lymphoproliferative disease
- “Sexual Frenzy”
Cyclosporine Monitoring

Baseline
- 2 serum creatinines
- 2 BP’s
- Chem screen with Mg++, lipids, CBC

Followup
- BP, creatinine, Chem screen with Mg++, lipids, CBC
K+ : Rx:HCTZ 50 qod
Mg#: Rx:Mg# supplement
bilirubin: Rx: None
uric acid: Rx: None
lipids: Pravastatin
Drug interactions with lipid-lowering drugs: mechanisms and clinical relevance.

Neuvonen PJ, et al.

Pravastatin
10, 20, 40 and 80 mg tabs

Start at 40mg po daily
Can increase up to 80mg
43 y.o. WF – 50% Psoriasis
Failed UVB
PUVA x 7 yrs – 400 therapies
6 SCC’s
Hyperlipidemia
ETOH – 12 units/week
Hysterectomy
Options:

1) More PUVA
2) Cyclosporine
3) TNF-α blocker
4) Ustekinumab
5) Anti-IL-17 antibody
6) Methotrexate
7) Acitretin + Biologic
8) Apremilast
Effects of gemfibrozil (Lopid) on hyperlipidemia in acitretin-treated patients. Results of a double-blind cross-over study.

Prevention of Skin Cancer and Reduction of Keratotic Skin Lesions During Acitretin Therapy in Renal Transplant Recipients: A Double-Blind, Placebo-Controlled Study.


- Acitretin 30 mg/day
Multiple squamous cell carcinomas in a psoriatic patient following high-dose photochemotherapy and cyclosporin treatment: response to long-tern acitretin maintenance.

Acitretin Monitoring

**Baseline**
- Chem screen with lipids, CBC

**Followup**
- Chem screen with lipids
27 yo ♀ with severe palm and sole psoriasis, h/o poorly controlled dm, creatinine 2.6

1) Methotrexate
2) Cyclosporine
3) Acitretin
4) TNF blocker
5) Ustekinumab
6) Anti-IL-17 antibody
7) Apremilast
Successful treatment of hand and foot psoriasis with infliximab.
Di Lernia V, Guareschi E.

Severe psoriasis pustulosa palmaris et plantaris (Barber-Königsbeck) treated successfully with soluble tumour necrosis factor receptor fusion protein (etanercept).
Kasche A, et al
Successful treatment of recalcitrant palmoplantar psoriasis with etanercept.
Weinberg JM.
Clinical and patient-reported improvements of hand and/or foot psoriasis with ADA 40 mg qow: Subanalysis of REACH

- Subanalysis of REACH study looking at elements of erythema, scaling, induration and fissuring (ESIF) score along with DLQI
An investigator-initiated, open-label study evaluating the efficacy and safety of UST in patients with moderate-to-severe palmar/plantar psoriasis

- 24 subjects with palmar/plantar psoriasis with PGA ≥3 treated with FDA-approved dose of UST using weight-based dosing
- Report of 20/24 subjects, 11 in 45-mg dose, 9 in 90-mg dose. Mean weight of subjects not reported

Shimrat Y, et al. AAD 2012: P4733; Study sponsored by Centocor
Investigator-initiated, open-label trial of ustekinumab for the treatment of moderate-to-severe palmoplantar psoriasis.

J Dermatolog Treat. 2012 May 8. [Epub ahead of print]

7/20 → clear (90 mg:6/9; 45mg:1/11)
12/20 → >2point PGA improvement
More than Half of All Subjects on Secukinumab 300 mg Achieved Clear/Almost Clear Palms and Soles at 1.5 Years

Palmoplantar disease improved by approximately 70% at 1.5 years in subjects receiving secukinumab 300 mg
UNCOVER-3: Ixekizumab in patients with palmoplantar involvement: ppPASI 75 response rates

- These patients have plaque psoriasis of the hands and feet, this does not address efficacy in pustular disease nor patients with predominantly palmoplantar disease.
Lassus A, Geiger JM.
Apremilast in nail, scalp and palmoplantar psoriasis (ESTEEM 2)

- Subanalysis of ESTEEM 2
- Scalp Physicians Global Assessment (ScPGA), and Palmoplantar Physicians Global Assessment (PPPGA)

![Graph showing NAPSI 50 response, ScPGA response, and PPPGA response over weeks 16 and 32, with P values](image)

Crowley J, et al. EADV 2014, P1687
Apremilast

- No guidelines
- No monitoring requirements
- Pregnancy category C
- Nausea & diarrhea
- Start at low dose to minimize GI side effects