Psoriasis: Which Drug for Which Patient?

Mark Lebwohl, MD

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And Chairman
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Icahn School of Medicine at Mount Sinai
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.
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Drug-Induced SLE Associated with Etanercept Therapy

• 4 patients.
• Manifestations including fever, arthritis, discoid skin changes, rash, pleuritic pain, ANA, anti-dsDNA, anti-histone, hypocomplementememia, anti-Sm, anti-RNP.
• No baseline serologies.
• All resolved with discontinuation of etanercept and/or addition of corticosteroids.

## TNF- Inhibitor Induced Lupus

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<th>Classic DILE(^1)</th>
<th>TNF-α inhibitor DILE(^2)</th>
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<tr>
<td>ANA</td>
<td>&gt;95%</td>
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<td>dsDNA</td>
<td>&lt;1%</td>
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<td>Antihistone</td>
<td>&gt;95%</td>
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<td>Decreased complement</td>
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<td>Rash</td>
<td>27%</td>
<td>72%</td>
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1. Benucci et al Clin Rheumatol 27:91-95
Regression of subacute cutaneous lupus erythematosus in a patient with rheumatoid arthritis treated with a biologic tumor necrosis factor alpha-blocking agent: comment on the article by Pisetsky and the letter from Aringer et al.

Fautrel B, Foltz V, Frances C, Bourgeois P, Rozenberg S.

• ↓ proteinuria, arthritis, C4
• ↑ autoantibodies
Treatment of coexistent psoriasis and lupus erythematosus.
Varada S, Gottlieb AB, Merola JF, Saraiya AR, Tintle SJ.

“Anti-TNF-α agents, ustekinumab, and abatacept may be valid treatment options for patients with concomitant LE and psoriasis. Clinical lupus flares in LE patients treated with TNF-α inhibitors were infrequent.”
Apremilast for discoid lupus erythematosus: results of a phase 2, open-label, single-arm, pilot study.

De Souza A, Strober BE, Merola JF, Oliver S, Franks AG Jr.

A 2 year, open ended trial of methotrexate in systemic lupus erythematosus.
Wilson K, Abeles M.

Discoid lupus erythematosus: successful treatment with oral methotrexate.
Goldstein E, Carey W.
Hypertrophic lupus erythematosus treated successfully with acitretin as monotherapy.

Efficiency of acitretin in the treatment of cutaneous lupus erythematosus.

TNF neutralization in MS: results of a randomized, placebo-controlled multicenter study.

- MS exacerbations ↑ with lenercept.
Demyelination occurring during anti-tumor necrosis factor alpha therapy for inflammatory arthritides.

Mohan N, et al.

- 17 – etanercept, 2 – infliximab
- partial or complete resolution on d/c
- 1 positive rechallenge

- UST → no effect on MS
Activity of secukinumab, an anti-IL-17A antibody, on brain lesions in RRMS: results from a randomized, proof-of-concept study.

Havrdová E, et al
Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn's disease: unexpected results of a randomised, double-blind placebo-controlled trial.

Hueber W, Sands BE, et al

Secukinumab not effective
No Definitive Role of Secukinumab in Crohn’s Disease

Entire treatment period – exposure-adjusted (52 weeks)

• Potential involvement of IL-17 in Crohn’s disease however published trials have not shown clinical benefit or disease exacerbation, consistent with Novartis Phase II in Crohn’s

• Phase III incidence rate as expected with psoriasis
  – No dose relationship between secukinumab doses
  – All cases with Crohn’s disease had prior history

<table>
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<tr>
<th>Based on all AEs</th>
<th>AIN457 300 mg (n=1410) n (IR) [95% CI]</th>
<th>AIN457 150 mg (n=1395) n (IR) [95% CI]</th>
<th>Placebo (n=793) n (IR) [95% CI]</th>
<th>Etanercept (n=323) n (IR) [95% CI]</th>
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<td>Inflammatory bowel disease</td>
<td>3 (0.26) [0.05, 0.75]</td>
<td>4 (0.35) [0.10, 0.90]</td>
<td>0 (0.00) [0.0, 1.83]</td>
<td>1 (0.34) [0.01, 1.90]</td>
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<td>Colitis ulcerative</td>
<td>2 (0.17) [0.02, 0.61]</td>
<td>2 (0.18) [0.02, 0.63]</td>
<td>0 (0.00) [0.0, 1.83]</td>
<td>1 (0.34) [0.01, 1.90]</td>
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<td>Crohn’s disease*</td>
<td>0 (0.00) [0.0, 0.31]</td>
<td>2 (0.18) [0.02, 0.63]</td>
<td>0 (0.00) [0.0, 1.83]</td>
<td>0 (0.00) [0.0, 1.26]</td>
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<td>Anal fistula**</td>
<td>1 (0.08) [0.0, 0.47]</td>
<td>0 (0.00) [0.0, 0.32]</td>
<td>0 (0.00) [0.0, 1.83]</td>
<td>0 (0.00) [0.0, 1.26]</td>
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IR=Exposure-adjusted incidence rate per 100 patient-years.
A third case of Crohn’s disease occurred in study A2211E1-150 mg Start of Relapse arm
** Not associated with inflammatory bowel disease
Does exposure to isotretinoin increase the risk for the development of inflammatory bowel disease?
A meta-analysis.


NO
Isotretinoin and inflammatory bowel disease: trial lawyer misuse of science and FDA warnings.

Tenner S.

Isotretinoin, acne, and Crohn's disease: a convergence of bad skin, bad science, and bad litigation creates the perfect storm.


Etanercept and Hepatitis C.
Pritchard C.
Journal of Clinical Rheumatology.

- 1 patient with rheumatoid arthritis & hepatitis C
- etanercept $\rightarrow$ ↑ LFT's and ↑ viral titers
- d/c etanercept $\rightarrow$ improved liver function

- **ETN (21), ADA (4), UST (4), IFX (2)**
- **HCV (20), HBV (5)**
• ↑LFT’s 2x in one pt (ETN)
• 2 pt’s ↑viral load during followup.
• 2pt’s →hepatocellular ca. (ETN)

“Biologic therapy was effective and safe for the majority of our patients with HCV and HBV infection”

Navarro R. et al.
Etanercept as an adjuvant to interferon and ribavirin in treatment-naive patients with chronic hepatitis C virus infection: a phase 2 randomized, double-blind, placebo-controlled study.
Zein NN, for the Etanercept Study Group.

- HCV, RNA was absent in 63% (12/19) etanercept patients, 32% (8/25) placebo patients.
- Patients receiving etanercept had lower frequency of most adverse events.
- Liver bx regression of fibrosis: 6/11(55%) vs 2/6(33%)

- Hepatitis C:
  - Infliximab → No worsening of LFT’s or vital titers by PCR.
Hepatotoxicity

Severe hepatic reactions, including acute liver failure, jaundice, hepatitis and cholestasis have been reported rarely in postmarketing data in patients receiving **REMICADE®**. Autoimmune hepatitis has been diagnosed in some of these cases. Severe hepatic reactions occurred between two weeks to more than a year after initiation of **REMICADE®**. Elevations in hepatic aminotransferase levels were not noted prior to discovery of the liver injury in many of these cases. Some of these cases were fatal or necessitated liver transplantation. Patients with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or marked liver enzyme elevations (e.g., \( >5 \) times the upper limit of normal) develops, **REMICADE®** should be discontinued, and a thorough investigation of the abnormality should be undertaken. As with other immunosuppressive drugs, use of **REMICADE®** has been associated with reactivation of hepatitis B in patients who are chronic carriers of this virus (i.e., surface antigen positive). Chronic carriers of hepatitis B should be appropriately evaluated and monitored prior to the initiation of and during treatment with **REMICADE®**. In clinical trials, mild or moderate elevations of ALT and AST have been observed in patients receiving **REMICADE®** without progression to severe hepatic injury (see ADVERSE REACTIONS, Hepatotoxicity).
Induction of clinical remission with adalimumab-methotrexate combination therapy in a patient with rheumatoid arthritis and concomitant hepatitis C virus infection.
Noguchi O, Gibo Y

Frider B, Bruno A, Ponte M, Amante M.

Use of tumor necrosis factor-alpha (TNF-alpha) antagonists infliximab, etanercept, and adalimumab in patients with concurrent rheumatoid arthritis and hepatitis B or hepatitis C: a retrospective record review of 11 patients.
Li S, Kaur PP, Chan V, Berney S.
Two patients showed a transient elevation in AST and/or ALT from normal, but in all 11 patients, AST and ALT levels were within one time the upper range of normal at the conclusion of the study.

No significant increase in viral load was seen except one patient who showed a fourfold increase from baseline.

“Use of these agents in patients with HBV or HCV may be associated with a transient transaminitis but appears to be safe overall. In both groups, frequent monitoring of serum transaminase levels and viral load is essential.”

The safety profile of ustekinumab in the treatment of psoriasis patients with concurrent hepatitis B or hepatitis C.
Chiu, H-Y et al.

- Reactivation of HCV and hepatocellular ca in 1/4 pts rx’d with UST
- No ↑ in ALT, AST
Psoriasis treated with ustekinumab in a patient with hepatitis C.

Abuchar A, Vitiello M, Kerdel FA.
Safety of Secukinumab in Hepatitis B Virus
SL Bevans, TT Mayo, BE Elewski, in press

- Reports of HBV infection (5 patients), HCV infection (3 patients), and HBV and HCV co-infection (1 patient), all without viral reactivation or significant elevation in liver enzymes.
Apremilast for a psoriasis patient with HIV and hepatitis C.

Reddy SP, Shah VV, Wu JJ.

Complications in methotrexate treatment of psoriasis with particular reference to liver fibrosis.

- hepatic fibrosis in 9/38 (24%) after 5 years
Does cyclosporine have a beneficial effect on the course of chronic hepatitis C infection after renal transplantation?

- “…HCV infection is not harmful to liver histology in more than 50% of renal transplant patients with grafts functioning more than 6 years. Cyclosporine might have beneficial effects on the natural course of HCV infection”


Specific inhibition of hepatitis C virus replication by cyclosporin A.

- Only 3 improved
- 1 case of hepatotoxicity of CsA
The role of different immunosuppression in the long-term histological outcome of HCV reinfection after liver transplantation for HCV cirrhosis.


- cyclosporine associated with recurrence & progression of hepatitis C
- need for retransplantation in 10-25% of patients within 5 years
Reactivation of chronic hepatitis C after withdrawal of immunosuppressive therapy.
Gruber A, Lundberg LG, Bjorkholm M. 

Activation of hepatitis C virus following immunosuppressive treatment.
Effects of acitretin on the liver

- No hepatotoxicity on liver bx after 2 yrs
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Which of the following treatments would be ideal for a patient with severe psoriasis, multiple sclerosis and Crohn disease?

A) Certolizumab
B) Brodalumab
C) Acitretin
D) Infliximab
E) Ustekinumab
Reasons to Become a Registry Investigator

- Contribute to education/clinical knowledge of the psoriasis community
- Opportunity to establish a database of your patient population
- Academic recognition and publication opportunities
- Supplement existing insurance fee schedules
  - Site compensation is $525 (including $25 for patient) per Enrollment visit and $350 (including $25 for patient) per biannual Follow Up visit
If you are interested in participating in the Psoriasis Registry as a research investigator, please email psoriasis@corrona.org or visit www.corrona.org or call 508.408.5432