Do You Know JAK?

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And Chairman  
Kimberly and Eric J. Waldman  
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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 and ViDac.

Dr. Lebwohl is also a consultant for Allergan, Boehringer-Ingelheim, Leo and Promius.
Intramuscular triamcinolone acetonide: An undervalued option for refractory alopecia areata.
Seo J, et al.
Short-term use of oral corticosteroids was linked to increased risk for sepsis, VTE, and fractures.
Rowland K.

- median steroid use 6 days (327,452 users vs 1,221,493 nonusers)
- IRR for sepsis, VTE, fractures over 5-30/31-90 days:
  - sepsis: 5.30 / 2.91
  - VTE: 3.33 / 1.44
  - fractures: 1.87 / 2.07
Inhibiting Janus kinases to treat alopecia areata.
Divito SJ, Kupper TS
Transient efficacy of tofacitinib in alopecia areata universalis.
Anzengruber F, et al.

A case report highlighting the effective treatment of alopecia universalis with tofacitinib in an adolescent and adult patient.
Patel Nu, et al.
Ruxolitinib-induced reversal of alopecia universalis in a patient with essential thrombocytethemia. 
Pieri L, Guglielmelli P, Vannucchi AM. 

Complete regrowth of beard hair with ruxolitinib in an alopecia universalis patients. 
Ramot Y, Zlotogorski A. 
Skin Appendage Disord. 2018; 4(2) : 122-4.

• Alopecia universalis 11 years 
• Regrew beard with ruxolitinib 20 bid
Topical ruxolitinib for the treatment of alopecia universalis.
Craiglow BG, Tavares D, King BA.

- Ruxolitinib 0.6% cream bid
- 10% regrowth in 12 weeks

- “significant” regrowth in 1 patient
- Partial regrowth in 2 more patients
Alopecia universalis unresponsive to treatment with tofacinitib: report of a case with a brief review of the literature.

A case of topical ruxolitinib treatment failure in alopecia areata.
Deeb M, Beach RA.

- 77% → clinical response
- 58% → > 50% change in SALT score over 4-18mos
- AA > universalis or totalis (81.9% vs 59.0%)
Median % change SALT score:
Peribulbar inflammation: 32.9%
No inflammation: 1.2%
Oral ruxolitinib induces hair regrowth in patients with moderate-to-severe alopecia areata.

Reversal of Alopecia Areata Following Treatment With the JAK1/2 Inhibitor Baricitinib.
Recovery of nail dystrophy potential new therapeutic indication of tofacitinib.  
Jaller JA, et al.  

Tofacitinib citrate for the treatment of nail dystrophy associated with alopecia universalis.  
Dhayalan A, King BA.  
Nail involvement in patients with moderate-to-severe alopecia areata treated with oral tofacitinib.
Lee J, et al.

- 11/15 patients with nail changes of AA improved with tofacitinib beginning at a median of 5 months
Rapid repigmentation of vitiligo using tofacitinib plus low-dose, narrowband UV-B phototherapy.
Kim SR, et al.
*JAMA Dermatol.* 2018;154(3):370-1.
Repigmentation in vitiligo using the Janus kinase inhibitor tofacitinib may require concomitant light exposure.

• 5/10 patients repigmented at sites of sun or NB UVB exposure
Treatment of vitiligo with the topical Janus kinase inhibitor ruxolitinib.
Rothstein B, et al.

- 4/11 → ↑ 76% facial VASI w. 20
  (95% CI 53-99%; P = .001)
- 23%↑VASI in all patients w.20 (95% CI 4-43%; P = .02).
- 3/8 patients responded on body surfaces
- 1/8 patients responded on acral surfaces.

- 37.6% ↑ VASI
- 5/8 >0.5% on face → ↑facial VASI 92% at w.52
- 3/6 → 12.6% ↑ VASI nonacral UE’s
- 2/3 (both had UVB) → 16.7% ↑ VASI trunk
- One → sl. Acral repigmentation

Aggression behaviour induced by oral administration of the Janus-kinase inhibitor tofacitinib, but not oclacitinib, under stressful conditions.
Fukuyama T, et al.

Phase 2 study of topical JTE-052 in Japanese patients with moderate to severe AD: Primary endpoint

Percent change from baseline in m-EASI score over time

- **Vehicle**
- **JTE-052 0.25%**
- **JTE-052 0.50%**
- **JTE-052 1.00%**
- **JTE-052 3.00%**
- **Tacrolimus (open label)**

*P=0.0006; †P<0.0001; m-EASI, modified EASI; values obtained after use of rescue medication were excluded from the analyses of weekly percent change

Nakagawa H, et al. EADV 2017, P2118 Sponsored by Pharmaceutical Division, Japan Tobacco Inc.
Phase 2 study of topical JTE-052 in Japanese patients with moderate to severe AD: Safety

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Vehicle (n=32)</th>
<th>JTE-052 0.25% (n=69)</th>
<th>JTE-052 0.5% (n=65)</th>
<th>JTE-052 1% (n=66)</th>
<th>JTE-052 3% (n=65)</th>
<th>JTE-052 total (n=265)</th>
<th>Tacrolimus (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEs</td>
<td>5 (15.6)</td>
<td>13 (18.8)</td>
<td>12 (18.5)</td>
<td>14 (21.2)</td>
<td>12 (18.5)</td>
<td>51 (19.2)</td>
<td>13 (43.3)</td>
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<tr>
<td>Severe AE</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Adverse drug reactions</td>
<td>0</td>
<td>3 (4.3)</td>
<td>4 (6.2)</td>
<td>6 (9.1)</td>
<td>3 (4.6)</td>
<td>16 (6.0)</td>
<td>5 (16.7)</td>
</tr>
<tr>
<td>Serious adverse drug reaction</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Discontinuation due to AEs</td>
<td>0</td>
<td>1 (1.4)</td>
<td>1 (1.5)</td>
<td>1 (1.5)</td>
<td>0</td>
<td>3 (1.1)</td>
<td>1 (3.3)</td>
</tr>
</tbody>
</table>

AEs in ≥2 patients in any treatment group

<table>
<thead>
<tr>
<th>AEs</th>
<th>Vehicle (n=32)</th>
<th>JTE-052 0.25% (n=69)</th>
<th>JTE-052 0.5% (n=65)</th>
<th>JTE-052 1% (n=66)</th>
<th>JTE-052 3% (n=65)</th>
<th>JTE-052 total (n=265)</th>
<th>Tacrolimus (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>2 (6.3)</td>
<td>2 (2.9)</td>
<td>3 (4.6)</td>
<td>2 (3.0)</td>
<td>2 (3.1)</td>
<td>9 (3.4)</td>
<td>0</td>
</tr>
<tr>
<td>Acne</td>
<td>0</td>
<td>1 (1.4)</td>
<td>0</td>
<td>0</td>
<td>3 (4.6)</td>
<td>4 (1.5)</td>
<td>1 (3.3)</td>
</tr>
<tr>
<td>Furuncle</td>
<td>0</td>
<td>0</td>
<td>2 (3.1)</td>
<td>1 (1.5)</td>
<td>1 (1.5)</td>
<td>4 (1.5)</td>
<td>1 (3.3)</td>
</tr>
<tr>
<td>Folliculitis</td>
<td>0</td>
<td>0</td>
<td>1 (1.5)</td>
<td>0</td>
<td>2 (3.1)</td>
<td>3 (1.1)</td>
<td>0</td>
</tr>
<tr>
<td>Application site acne</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (3.0)</td>
<td>1 (1.5)</td>
<td>3 (1.1)</td>
<td>0</td>
</tr>
<tr>
<td>C-reactive protein increase</td>
<td>0</td>
<td>1 (1.4)</td>
<td>0</td>
<td>2 (3.0)</td>
<td>0</td>
<td>3 (1.1)</td>
<td>0</td>
</tr>
<tr>
<td>KVE</td>
<td>0</td>
<td>1 (1.4)</td>
<td>0</td>
<td>2 (3.0)</td>
<td>0</td>
<td>3 (1.1)</td>
<td>0</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>0</td>
<td>2 (2.9)</td>
<td>0</td>
<td>1 (1.5)</td>
<td>0</td>
<td>3 (1.1)</td>
<td>1 (3.3)</td>
</tr>
<tr>
<td>Contusion</td>
<td>0</td>
<td>3 (4.3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3 (1.1)</td>
<td>0</td>
</tr>
<tr>
<td>Application site pain</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (1.5)</td>
<td>0</td>
<td>1 (0.4)</td>
<td>3 (10.0)</td>
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<tr>
<td>Application site irritation</td>
<td>0</td>
<td>0</td>
<td>1 (1.5)</td>
<td>0</td>
<td>0</td>
<td>1 (0.4)</td>
<td>2 (6.7)</td>
</tr>
</tbody>
</table>

- Across all groups, there were no deaths or serious AEs
- An interesting active topical in development with a comparison tacrolimus group
- Efficacy appears similar to topical tofacitinib

Nakagawa H, et al. EADV 2017, P2118 Sponsored by Pharmaceutical Division, Japan Tobacco Inc.
Treatment of recalcitrant atopic dermatitis with the oral Janus kinase inhibitor tofacitinib citrate.
Levy LL, Urban J, King BA.

Phase 2 study of baricitinib in adults with moderate to severe AD: EASI 50 through Week 16

EASI 50 at Week 16

Change from baseline in EASI score over time

*P<0.05; †P≤0.01; ‡P≤0.001; aMixed-effects model of repeated measures; bLast observation is Week 16 LOCF

Guttman-Yassky E, et al. EADV 2017, FC04.01 Sponsored by Eli Lilly and Company
Phase 2 study of baricitinib in adults with moderate to severe AD: SCORAD through 16 weeks

**SCORAD Total**

- Placebo + TCS
- BAR 2 mg + TCS
- BAR 4 mg + TCS

**Change from baseline (%)**

- SCORAD Total
- SCORAD pruritus
- SCORAD sleep loss

*P<0.05, †P≤0.01, ‡P≤0.001; aLast observation is Week 16 LOCF; Analysis using mixed-effect model of repeated measures and LOCF

Guttman-Yassky E, et al. EADV 2017, FC04.01 Sponsored by Eli Lilly and Company
Phase 2b trial of upadacitinib in adults with moderate to severe AD:
Primary and key secondary endpoints at Week 16

Primary endpoint:
% change in EASI score

<table>
<thead>
<tr>
<th>Group</th>
<th>EASI 75</th>
<th>EASI 90</th>
<th>IGA 0/1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=39)</td>
<td>23</td>
<td>29</td>
<td>10</td>
</tr>
<tr>
<td>UPD 7.5 mg (n=42)</td>
<td>39</td>
<td>52</td>
<td>14</td>
</tr>
<tr>
<td>UPD 15 mg (n=42)</td>
<td>62</td>
<td>69</td>
<td>14</td>
</tr>
<tr>
<td>UPD 30 mg (n=42)</td>
<td>74</td>
<td>69</td>
<td>14</td>
</tr>
</tbody>
</table>

Key secondary endpoints:
Responder rates

<table>
<thead>
<tr>
<th>Group</th>
<th>EASI 75</th>
<th>EASI 90</th>
<th>IGA 0/1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=41)</td>
<td>22</td>
<td>29</td>
<td>2</td>
</tr>
<tr>
<td>UPD 7.5 mg (n=42)</td>
<td>39</td>
<td>52</td>
<td>14</td>
</tr>
<tr>
<td>UPD 15 mg (n=42)</td>
<td>62</td>
<td>69</td>
<td>14</td>
</tr>
<tr>
<td>UPD 30 mg (n=42)</td>
<td>74</td>
<td>69</td>
<td>14</td>
</tr>
</tbody>
</table>

Key secondary endpoint:
% change in pruritus/itch NRS

<table>
<thead>
<tr>
<th>Group</th>
<th>EASI 75</th>
<th>EASI 90</th>
<th>IGA 0/1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=37)</td>
<td>10</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>UPD 7.5 mg (n=40)</td>
<td>40</td>
<td>48</td>
<td>40</td>
</tr>
<tr>
<td>UPD 15 mg (n=37)</td>
<td>48</td>
<td>48</td>
<td>48</td>
</tr>
<tr>
<td>UPD 30 mg (n=42)</td>
<td>69</td>
<td>69</td>
<td>69</td>
</tr>
</tbody>
</table>

*P<0.05, †P<0.01, ‡P<0.001 vs placebo
Itch rated from 0 (no itch) to 10 (worst imaginable itch)

- Serious AEs occurred in 2/1/0 patients in the 7.5/15/30 mg groups and 1 patient in the placebo group
- No herpes zoster, malignancies, deaths or cases of pulmonary embolism or deep vein thrombosis were reported

- Dose response effect seen with all endpoints including IGA 0/1 and NRS response
- This study has exciting results and we are looking forward to seeing baseline and safety data

The use of JAKs by different cytokines

**JAK1**
- \(\gamma\)c family: IL-2, IL-4, IL-7, IL-9, IL-15
- gp130 family: IL-6, IL-11, OSM, LIF
- IFN\(\alpha/\beta\), IFN\(\gamma\), IL-10

**JAK2**
- gp130 family: IL-6, IL-11, OSM, LIF
- \(\beta\)c family: IL-3, IL-5, GM-CSF
- EPO, TPO, IFN\(\gamma\)
- IL-12/IL-23

**JAK3**
- \(\gamma\)c family: IL-2, IL-4, IL-7, IL-9, IL-15

**TYK2**
- gp130 family: IL-6, IL-11, OSM, LIF
- IFN\(\alpha/\beta\)
- IL-12/IL-23

OSM, oncostatin M; LIF, leukemia inhibitory factor; GM-CSF, granulocyte macrophage colony-stimulating factor; EPO, erythropoietin; TPO, thrombopoietin
Comparison of tofacitinib vs ETN or PBO in moderate to severe chronic plaque psoriasis: Phase 3 RCT

% patients achieving a PASI 75 response through Week 12 (NRI)

% patients achieving a PASI 90 response through Week 12 (NRI)

% patients achieving a PGA response through Week 12 (NRI)

Valenzuela F, et al. AAD 2014, Late breaking oral presentation Sponsored by Pfizer
Tofacitinib or adalimumab versus placebo for psoriatic arthritis.
Mease P, et al.
WARNING: SERIOUS INFECTIONS AND MALIGNANCY
See full prescribing information for complete boxed warning.

- Serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections, have occurred in patients receiving XELJANZ. (5.1)
- If a serious infection develops, interrupt XELJANZ/XELJANZ XR until the infection is controlled. (5.1)
- Prior to starting XELJANZ/XELJANZ XR, perform a test for latent tuberculosis; if it is positive, start treatment for tuberculosis prior to starting XELJANZ/XELJANZ XR. (5.1)
- **Monitor all patients for active tuberculosis during treatment** even if the initial latent tuberculosis test is negative. (5.1)
- Lymphoma and other malignancies have been observed in patients treated with XELJANZ. Epstein Barr Virus-associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with XELJANZ and concomitant immunosuppressive medications. (5.2)
Psoriatic Arthritis
Recommended dose of XELJANZ is 5 mg twice daily, used in combination with nonbiologic DMARDs. (2.2)
Recommended dose of XELJANZ XR is 11 mg once daily, used in combination with nonbiologic DMARDs. (2.2)
Recommended dose in patients with moderate and severe renal impairment and moderate hepatic impairment is XELJANZ 5 mg once daily. (2.5, 8.7, 8.8)
Use of XELJANZ/ XELJANZ XR in patients with severe hepatic impairment is not recommended. (2.5, 8.7)

• Interacts with cytochrome P4503A
### Table 1: Dose Adjustments for Lymphopenia

<table>
<thead>
<tr>
<th>Lab Value (cells/mm³)</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocyte count greater than or equal to 500</td>
<td>Maintain dose</td>
</tr>
<tr>
<td>Lymphocyte count less than 500 (Confirmed by repeat testing)</td>
<td>Discontinue XELJANZ/XELJANZ XR</td>
</tr>
</tbody>
</table>

### Table 2: Dose Adjustments for Neutropenia

<table>
<thead>
<tr>
<th>Lab Value (cells/mm³)</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC greater than 1000</td>
<td>Maintain dose</td>
</tr>
</tbody>
</table>
| ANC 500–1000                              | For persistent decreases in this range, interrupt dosing until ANC is greater than 1000  
|                                           |   - When ANC is greater than 1000, resume XELJANZ 5 mg twice daily/XELJANZ XR 11 mg once daily |
| ANC less than 500 (Confirmed by repeat testing) | Discontinue XELJANZ/XELJANZ XR                                               |
Table 3: Dose Adjustments for Anemia

<table>
<thead>
<tr>
<th>Low Hemoglobin Value [see Warnings and Precautions (5.4)]</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than or equal to 2 g/dL decrease and greater than or equal to 9.0 g/dL</td>
<td>Maintain dose</td>
</tr>
<tr>
<td>Greater than 2 g/dL decrease or less than 8.0 g/dL</td>
<td>Interrupt the administration of XELJANZ/XELJANZ XR until hemoglobin values have normalized</td>
</tr>
<tr>
<td>(Confirmed by repeat testing)</td>
<td></td>
</tr>
</tbody>
</table>

**Liver Enzyme Elevations**

Treatment with XELJANZ was associated with an increased incidence of liver enzyme elevation compared to placebo. Most of these abnormalities occurred in studies with background DMARD (primarily methotrexate) therapy.

Routine monitoring of liver tests and prompt investigation of the causes of liver enzyme elevations is recommended to identify potential cases of drug-induced liver injury. If drug-induced liver injury is suspected, the administration of XELJANZ/XELJANZ XR should be interrupted until this diagnosis has been excluded.

**Lipid Elevations**

Treatment with XELJANZ was associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol. Maximum effects were generally observed within 6 weeks. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined.

Assessment of lipid parameters should be performed approximately 4–8 weeks following initiation of XELJANZ/XELJANZ XR therapy.
Monitoring Recommendations for Tofacitinib

- Tb test baseline and “per applicable guidelines” (annually)
- CBC + plts baseline; after 4-8 weeks; q3mos
- LFT’s “routine monitoring” – baseline and q3-6mos
- Lipids – baseline and at 4-8 weeks