JAK inhibitors in dermatology: what to know about these “new” kids on the block

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• Research support: Pfizer, Incyte, Advanced Cell Diagnostics/Bio-techne, AbbVie

• Consulting fees: Eli Lilly, Incyte, Pfizer, Twi Biotechnology

• Licensing fees: EMD/Millipore/Sigma

• I will discuss off label use of JAK inhibitors
My introduction to JAK inhibitors in dermatology (2015 – 2018)

Killing Two Birds with One Stone: Oral Tofacitinib Reverses Alopecia Universalis in a Patient with Plaque Psoriasis

Journal of Investigative Dermatology (2014) 134, 2998-2999; doi:10.1038/jid.2014.264; published online 17 July 2014

J Invest Derm 2015: Craiglow and King

Alopecia areata is driven by cytotoxic T lymphocytes and is reversed by JAK inhibition

Nature Medicine 2014: Xing, Christiano, Clynes

Treatment of recalcitrant atopic dermatitis with the oral Janus kinase inhibitor tofacitinib citrate

JAAD 2015: Levy, King

Tofacitinib Treatment and Molecular Analysis of Cutaneous Sarcoidosis

NEJM 2018: Damsky, King

Brett King
JAK inhibitors in 2022

3 US approvals in atopic dermatitis

U.S. FDA Approves Pfizer’s CIBINQO® (abrocitinib) for Adults with Moderate-to-Severe Atopic Dermatitis

U.S. FDA Approves RINVOQ® (upadacitinib) to Treat Adults and Children 12 Years and Older with Refractory, Moderate to Severe Atopic Dermatitis

EMA recommends approval of baricitinib for atopic dermatitis

Incyte Announces U.S. FDA Approval of Opzelura™ (ruxolitinib) Cream, a Topical JAK Inhibitor, for the Treatment of Atopic Dermatitis (AD)

3 active breakthrough designations in alopecia areata

FDA Grants Fast Track Designation to Concert Pharmaceuticals’ CTP-543 for the Treatment of Alopecia Areata

Pfizer Receives Breakthrough Therapy Designation from FDA for PF-06651600, an oral JAK3 Inhibitor, for the Treatment of Patients with Alopecia Areata

Lilly Receives FDA Breakthrough Therapy Designation for Baricitinib for the Treatment of Alopecia Areata

Priority review for vitiligo

Ruxolitinib Cream Gets Priority Review for Vitiligo Treatment
Overview of today’s talk

• Part 1: What is JAK-STAT signaling?

• Part 2: What is a JAK inhibitor and why does it seem to “treat everything” in dermatology?

• Part 3: Why do JAK inhibitors have black box warnings and what are they?

• Part 4: How selective are “selective” JAK inhibitors and does it matter?
Part 1: What is JAK-STAT signaling?
What are cytokines?

- Secreted messenger molecules involved in:
  - Protective immunity
  - Autoimmunity / inflammation
  - Allergic disease
  - Hematopoiesis
  - Tissue repair
  - Growth
  - Metabolism

- Often (but not always) designated interleukin

- But not all are, e.g.
  - TNF-α
  - Interferon gamma (IFN-γ)
  - Erythropoietin (EPO)
  - Growth hormone (GH)
  - Prolactin

- Approximately 200 cytokines are known
Some cytokines signal via the JAK-STAT pathway while others do not

- About 57 (of ~200) cytokines signal via the JAK-STAT pathway

- Cytokines you may know that DO signal via JAK-STAT:
  - IL-2
  - IFN-α/β
  - IFN-γ
  - IL-15
  - IL-4/IL-13
  - IL-5
  - IL-12/IL-23

- Th1 (Type 1)

- Cytokines you may know that DO NOT signal via JAK-STAT:
  - IL-1β
  - TNF-α
  - IL-17
  - TGF-β

- Unexpected cytokines that signal via JAK-STAT!
  - Erythropoietin (EPO)
  - Thrombopoietin (TPO)
  - Growth hormone
  - Prolactin
  - Leptin
What is JAK-STAT signaling

JAK: Janus kinase

STAT: Signal Transducer and Activator of Transcription

Damsky et al. J All Clin Immunol 2020
How do we know cytokines and JAK-STAT signaling are important for immunity?
Severe Combined Immunodeficiency (SCID)

Dwyer et al 2019 Front Immunol 10: 263
JAK proteins are highly structurally similar

<table>
<thead>
<tr>
<th>Knockout phenotype</th>
<th>Expression Patterns</th>
<th>Key Cytokines</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>JAK1</strong></td>
<td>Lethal</td>
<td>IFN-α/β, IFN-γ, IL-2, IL-4, IL-15, IL-6 family, IL-10 family</td>
</tr>
<tr>
<td><strong>JAK2</strong></td>
<td>Lethal (erythropoiesis)</td>
<td>Widely expressed</td>
</tr>
<tr>
<td><strong>JAK3</strong></td>
<td>SCID</td>
<td>Immune specific</td>
</tr>
<tr>
<td><strong>TYK2 (JAK4)</strong></td>
<td>Infections</td>
<td>Widely expressed</td>
</tr>
</tbody>
</table>

JAKs are tyrosine kinases
JAKs are very structurally similar!

Hu et al. 2021. Signal Transduct Target Ther. 6:402
4 JAKs and 57 cytokines!

“Principles” of JAK inhibition:
- There is both specificity and redundancy in the system
- Blocking JAK proteins inherently affects >1 cytokine
- JAK1: many cytokines
- JAK2: hematopoiesis
  - EPO, TPO, G-CSF, etc
- JAK3: immune specific JAK
  - IL-2, IL-4, IL-15
- TYK2:
  - IL-12/23 – psoriasis
  - Type I IFN - lupus
There are 7 STAT genes

STATs are transcription factors - difficult to inhibit! Alteration can result in autoimmunity and/or immunodeficiency

<table>
<thead>
<tr>
<th>STAT</th>
<th>Genetic variation</th>
<th>Cytokines</th>
</tr>
</thead>
<tbody>
<tr>
<td>STAT1</td>
<td>Susceptible to mycobacteria/virus (GOF STAT1: CMC)</td>
<td>Interferons (IFNs)</td>
</tr>
<tr>
<td>STAT2</td>
<td>Immunodeficiency</td>
<td>Type I IFNs (α/β)</td>
</tr>
<tr>
<td>STAT3</td>
<td>Lethal in mice (LOF STAT3: Hyper IgE syndrome aka Job)</td>
<td>IL-6 family</td>
</tr>
<tr>
<td>STAT4</td>
<td>Polymorphisms, lupus, psoriasis</td>
<td>IL-12, IL-23, Type I IFNs (α/β)</td>
</tr>
<tr>
<td>STAT5A</td>
<td>Autoimmunity, immunodeficiency, dwarfism</td>
<td>IL-2, EPO, TOP, GM-CSF, GH</td>
</tr>
<tr>
<td>STAT5B</td>
<td>Polymorphisms, atopic diseases</td>
<td>IL-4, IL-13</td>
</tr>
</tbody>
</table>

Hu et al. 2021. Signal Transduct Target Ther. 6:402

CMC: Chronic mucocutaneous candidiasis
GOF: gain of function
LOF: loss of function
Summary Part 1

• Cytokines are secreted factors that regulate fundamental aspects of immunity (and other functions)
• Many (but not all) cytokines signal via the JAK-STAT pathway
• JAK-STAT signaling is important for regular immune function
• **JAK-STAT signaling is overactivated in auto-immune and inflammatory diseases regulated by cytokines**
• There is significant redundancy in JAK-STAT signaling components downstream of cytokines (57 cytokines and 4 JAKs)
• While there is some specificity, blocking JAKs would be predicted to affect many cytokines
Part 2: What is a JAK inhibitor and why does it seem to “treat everything” in dermatology?
JAK inhibition

- Is it even possible to inhibit JAK-STAT signaling given its essential role in immunity and other processes, including:
  - Hematopoiesis including erythropoiesis and thrombopoiesis
  - Growth hormone signaling
  - Leptin signaling
JAK inhibition is fundamentally different than biologics

Dose matters!

Doses of JAK inhibitors used to treat autoimmunity significantly lower than used in other settings explored during development

- e.g., tofacitinib 5 mg bid – autoimmunity
- vs. tofacitinib 30 mg bid – prevent organ transplant rejection
What JAK inhibitors are on the market now?
<table>
<thead>
<tr>
<th>Drug</th>
<th>Approved Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tofacitinib</td>
<td>RA, PSA, UC, JIA</td>
</tr>
<tr>
<td>Baricitinib</td>
<td>RA, COVID-19, AD (EU)</td>
</tr>
<tr>
<td>Upadacitinib</td>
<td>RA, AD</td>
</tr>
<tr>
<td>Abrocitinib</td>
<td>AD</td>
</tr>
<tr>
<td>Delgocitinib</td>
<td>AD (topical, Japan)</td>
</tr>
<tr>
<td>Filgotinib</td>
<td>RA (EU, Japan)</td>
</tr>
<tr>
<td>Ruxolitinib</td>
<td>GVHD, heme (topical AD, ? vitiligo)</td>
</tr>
<tr>
<td>Deucravacitinib</td>
<td>(trials – psoriasis)</td>
</tr>
<tr>
<td>Ritlecitinib</td>
<td>(trials – AA)</td>
</tr>
</tbody>
</table>

**JAK inhibitors have varying specificities and approvals**

RA: Rheumatoid arthritis  
PSA: Psoriatic arthritis  
UC: Ulcerative colitis  
JIA: Juvenile idiopathic arthritis  
AD: atopic dermatitis  
EU: European Union  
GVHD: graft-versus-host disease  
AA: alopecia areata  

**Diagram:**

- JAK1  
- JAK2  
- JAK3  
- TYK2

**Table:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>JAK1</th>
<th>JAK2</th>
<th>JAK3</th>
<th>TYK2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tofacitinib</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Baricitinib</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Upadacitinib</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Abrocitinib</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Delgocitinib</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Filgotinib</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ruxolitinib</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Deucravacitinib</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Ritlecitinib</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

**Notes:**

- RA: Rheumatoid arthritis  
- PSA: Psoriatic arthritis  
- UC: Ulcerative colitis  
- JIA: Juvenile idiopathic arthritis  
- AD: atopic dermatitis  
- EU: European Union  
- GVHD: graft-versus-host disease  
- AA: alopecia areata
JAK inhibitors have also shown promise in other settings with varying levels of evidence.
Exploratory indication: sarcoidosis

Cytokines:

**JAK-STAT dependent:**
- IFN-α/β
- IL-12
- IL-15
- GM-CSF
- IL-2
- IFN-γ
- IL-4
- IL-13
- IL-5
- IL-6
- IL-10

**JAK-STAT independent:**
- TNF-α
- IL-18
- *IL-17 family* (not pictured)

**Chemokines:**
- MIP (CCL3)
- MCP1 (CCL2)
Would a JAK inhibitor work to treat sarcoidosis?
48-year-old woman with long-standing sarcoidosis who had failed a number of therapies previously

A  Skin Disease before and during Treatment

<table>
<thead>
<tr>
<th>Before Treatment</th>
<th>During Treatment</th>
<th>Before Treatment</th>
<th>During Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>No treatment</td>
<td>tofacitinib 5 mg bid</td>
<td>No treatment</td>
<td>tofacitinib 5 mg bid</td>
</tr>
</tbody>
</table>
Histologic resolution of granulomas with tofacitinib

\[ p = \text{phosphorylated (activated)} \]
Similar efficacy was observed by us and others in additional patients in skin and beyond

Table I. A summary of the reported use of Janus kinase inhibitors to treat cutaneous and systemic sarcoidosis

<table>
<thead>
<tr>
<th>Drug</th>
<th>JAKs</th>
<th>Dose</th>
<th>α</th>
<th>β</th>
<th>Disease duration</th>
<th>Fitzpatrick type</th>
<th>Sex</th>
<th>Country</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral JAK inhibition</td>
<td>Tofacitinib JAK1/2/3</td>
<td>5 mg twice daily</td>
<td>1</td>
<td>CR</td>
<td>N/A</td>
<td>8 y</td>
<td>II</td>
<td>F</td>
<td>United States</td>
</tr>
<tr>
<td>Tofacitinib JAK1/2/3</td>
<td>5 mg twice daily</td>
<td>3</td>
<td>CR (3)</td>
<td>N/A</td>
<td>6-25 y</td>
<td>VI</td>
<td>2 F</td>
<td>United States</td>
<td>Damsky et al.4</td>
</tr>
<tr>
<td>Tofacitinib JAK1/2/3</td>
<td>5-10 mg twice daily</td>
<td>1</td>
<td>CR</td>
<td>CR</td>
<td>21 y</td>
<td>I</td>
<td>F</td>
<td>United States</td>
<td>Damsky et al.4</td>
</tr>
<tr>
<td>Tofacitinib JAK1/2/3</td>
<td>2.5-16 mg twice daily</td>
<td>5</td>
<td>CR/NCR (3), PR (2)</td>
<td>PR (3), N/A (2)</td>
<td>Not reported</td>
<td>White</td>
<td>F</td>
<td>Australia</td>
<td>Kerkemeyer et al.9</td>
</tr>
<tr>
<td>Tofacitinib JAK1/2/3</td>
<td>5 mg twice daily</td>
<td>5</td>
<td>N/A</td>
<td>PR (3), N/A (2)</td>
<td>1-5 y</td>
<td>4 Caucasian, 1 African American</td>
<td>United States</td>
<td>Friedman et al.10</td>
<td></td>
</tr>
<tr>
<td>Ruxolitinib JAK1/2</td>
<td>5 mg twice daily</td>
<td>1</td>
<td>CR</td>
<td>NCR</td>
<td>18 y</td>
<td>European ancestry</td>
<td>F</td>
<td>France</td>
<td>Rotenberg et al.10</td>
</tr>
<tr>
<td>Ruxolitinib JAK1/2</td>
<td>10 mg twice daily</td>
<td>1</td>
<td>CR</td>
<td>PR</td>
<td>1 y</td>
<td>VI</td>
<td>United States</td>
<td>Wei et al.11</td>
<td></td>
</tr>
<tr>
<td>Ruxolitinib JAK1/2</td>
<td>20 mg daily</td>
<td>1</td>
<td>N/A</td>
<td>CR</td>
<td>5 y</td>
<td>Not reported</td>
<td>F</td>
<td>France</td>
<td>Lewraut et al.12</td>
</tr>
<tr>
<td>Baricitinib JAK1/2</td>
<td>4 mg daily</td>
<td>1</td>
<td>N/A</td>
<td>CR</td>
<td>10 wk</td>
<td>Not reported</td>
<td>F</td>
<td>Brazil</td>
<td>Scheinberg et al.13</td>
</tr>
<tr>
<td>Topical JAK inhibition</td>
<td>Tofacitinib JAK1/2/3</td>
<td>2% ointment twice daily</td>
<td>1</td>
<td>PR</td>
<td>N/A</td>
<td>5 y</td>
<td>II</td>
<td>F</td>
<td>United States</td>
</tr>
<tr>
<td>Tofacitinib JAK1/2/3</td>
<td>2% ointment twice daily</td>
<td>1</td>
<td>PR</td>
<td>N/A</td>
<td>9 y</td>
<td>VI</td>
<td>M</td>
<td>United States</td>
<td>Alam et al.15</td>
</tr>
</tbody>
</table>

CR, Complete response; F, female; JAK, Janus kinase; M, male; N/A, not applicable; NCR, near complete response; PR, partial response.
Open label trial in 10 patients with sarcoidosis involving skin
• tofacitinib 5 mg twice daily for 6 months
• long-standing severe disease
Skin:
• 6 complete responses in skin
• 4 partial responses in skin
Internal:
• Most patients improved
Patients generally able to reduce or discontinue baseline immunosuppression (methotrexate, prednisone)

No significant AEs
Why did JAK inhibition work in sarcoidosis?

Primary mechanism:
• Inhibition of IFN-γ (JAK1/2)

Secondary mechanisms:
• IL-12 (JAK2/TYK2)
• IL-6 (JAK 1/2)
• IL-15 (JAK1/3)
• GM-CSF (JAK2)
So why do JAK inhibitors seem to “work” for everything?

- Ability to inhibit multiple key cytokines encompassing:
  - Type 1 (Th1) immunity: IL-2, IFN-\(\gamma\), IL-15
  - Type 2 (Th2) immunity: IL-4, IL-15, IL-13
  - Type 3 (eg Th17) immunity: IL-12, IL-23
- Inhibition of cytokines is simultaneous
- Cytokines are inhibited no matter what cell type they come from (as opposed to T cell directed immunosuppression)
- JAK inhibition provides robust inhibition of interferons- especially IFN-\(\gamma\) (marker: risk of zoster reactivation)
JAK inhibitors can treat "classic" and "non-classic" disease

- "Psoriasiform dermatitis" – both Th2 and Th17 components (if present) would be inhibited
- Patients with poly-autoimmunity and poly-inflammation (e.g. RA + AA) can be treated with a single agent

**Moving forward**
- Define key cytokines in each disease to most rationally select JAK inhibitors with varying specificity
Summary Part 2

- JAK inhibitors have demonstrate impressive activity in dermatologic diseases, many of which are historically recalcitrant to therapy.
- JAK inhibitors inhibit many cytokines simultaneously which may explain their efficacy.
- JAK inhibitors inhibit cytokines irrespective of the cell producing them.
- JAK inhibitors with different specificity may be preferable for different diseases depending on the underlying immunology.
Part 3: Why do JAK inhibitors have black box warnings and what are they?
Boxed warnings on JAK inhibitors

- Serious infections
- Mortality
- Malignancies
- Major adverse cardiovascular events (MACE)
- Thrombosis

- Boxed warnings apply to ALL available JAK inhibitors in US for inflammatory indications (both topical and oral)
• Study required by FDA given increased incidence of hyperlipidemia and cancers during tofacitinib development (e.g. in RA studies)

• Randomized, open-label, noninferiority, post-authorization, safety end-point trial ("ORAL Surveillance")

• Patients with RA treated with:
  • Tofacitinib 5 mg twice daily (n=1455)
  • Tofacitinib 10 mg twice daily (n=1456) → interim safety analysis 2019 → switch to 5 mg bid (but ITT analysis)
  • TNF-\(\alpha\) inhibitor (n=1451)
    • Adalimumab 40 mg every two weeks, OR
    • Etanercept 50 mg once weekly

• Coprimary endpoints
  • MACE
  • Cancers (excluding NMSC)

• Noninferiority definition: Hazard ratio: upper bound of 95% confidence interval \(\geq 1.8\) (tofacitinib both groups combined vs TNF-\(\alpha\) inhibitor)

• 333 sites in 20 countries (March 2014 – July 2020)

• Median follow-up: 4 years
Patients

- Active RA despite methotrexate
  - Background methotrexate was continued (unless modification was clinically indicated)
- 50 years or older with at least one additional CV risk factor
  - Current cigarette smoker
  - Hypertension
  - HDL < 40 mg/dL
  - Diabetes mellitus
  - Family history of premature coronary heart disease
  - Extra-articular RA
  - History of coronary artery disease

![Table 1: Demographic and Clinical Characteristics of the Patients at Baseline (Safety Analysis Population)](image)
MACE

- **MACE Definition:**
  - Death from cardiovascular causes
  - Non-fatal myocardial infarction
  - Non-fatal stroke

- **Cumulative estimated probability over 5.5 years:**
  - Tofacitinib combined: 5.8%
  - TNF-α: 4.8% of patients
MACE
(Stratified by age)

It appears the risk of MACE with tofacitinib is amplified in patients ≥65 years old.
MACE: unanswered questions

Mechanism: We don’t really know
• Lipid dependent?
• Direct effect if JAK inhibitor?
• Multifactorial?

Does JAK specificity matter: We don’t really know
• JAK1: widely expressed
• JAK2: widely expressed
• JAK3: immune restricted (but expressed on platelets)
• TYK2: widely expressed

Does underlying disease state matter: we don’t really know
Cancer

- Any cancer (excluding non-melanoma skin cancer)
- Cumulative estimated probability over 5.5 years:
  - Tofacitinib combined: 6.1%
  - TNF-α: 3.8% of patients
- HR: 1.48 (1.04-2.09)
- Most commonly lung cancer
- (NMSC also higher in the tofacitinib groups)
MACE (Stratified by age)
Cancer Mechanism: decreased tumor immunosurveillance?
**Table 2. Adverse Events (Safety Analysis Population, 28-Day On-Treatment Time).**

<table>
<thead>
<tr>
<th>Event</th>
<th>Tofacitinib, 5 mg Twice Daily (N = 1455)</th>
<th>Tofacitinib, 10 mg Twice Daily (N = 1456)</th>
<th>TNF Inhibitor (N = 1451)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event — no. (%)</td>
<td>1333 (91.6)</td>
<td>1344 (92.3)</td>
<td>1308 (90.1)</td>
</tr>
<tr>
<td>Serious adverse event — no. (%)</td>
<td>351 (24.1)</td>
<td>390 (26.8)</td>
<td>306 (21.1)</td>
</tr>
<tr>
<td>Discontinuation of trial treatment due to adverse event — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Permanent discontinuation</td>
<td>210 (14.4)</td>
<td>304 (20.9)</td>
<td>210 (14.5)</td>
</tr>
<tr>
<td>Temporary discontinuation</td>
<td>665 (45.7)</td>
<td>736 (50.5)</td>
<td>576 (39.7)</td>
</tr>
<tr>
<td>Adverse events of special interest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious infection — no. (%)</td>
<td>141 (9.7)</td>
<td>169 (11.6)</td>
<td>119 (8.2)</td>
</tr>
<tr>
<td>Hazard ratio vs. TNF inhibitor (95% CI)</td>
<td>1.17 (0.92–1.50)</td>
<td>1.48 (1.17–1.87)</td>
<td>Referent</td>
</tr>
<tr>
<td>Adjudicated opportunistic infection — no. (%)</td>
<td>39 (2.7)</td>
<td>44 (3.0)</td>
<td>21 (1.4)</td>
</tr>
<tr>
<td>Hazard ratio vs. TNF inhibitor (95% CI)</td>
<td>1.82 (1.07–3.09)</td>
<td>2.17 (1.29–3.66)</td>
<td>Referent</td>
</tr>
<tr>
<td>All herpes zoster, serious and nonserious — no. (%)</td>
<td>180 (12.4)</td>
<td>178 (12.2)</td>
<td>58 (4.0)</td>
</tr>
<tr>
<td>Hazard ratio vs. TNF inhibitor (95% CI)</td>
<td>3.28 (2.44–4.41)</td>
<td>3.39 (2.52–4.55)</td>
<td>Referent</td>
</tr>
<tr>
<td>Adjudicated hepatic event — no. (%)</td>
<td>46 (3.2)</td>
<td>72 (4.9)</td>
<td>35 (2.4)</td>
</tr>
<tr>
<td>Hazard ratio vs. TNF inhibitor (95% CI)</td>
<td>1.29 (0.83–2.00)</td>
<td>2.14 (1.43–3.21)</td>
<td>Referent</td>
</tr>
<tr>
<td>Adjudicated NMSC — no. (%)</td>
<td>31 (2.1)</td>
<td>33 (2.3)</td>
<td>16 (1.1)</td>
</tr>
<tr>
<td>Hazard ratio vs. TNF inhibitor (95% CI)</td>
<td>1.90 (1.04–3.47)</td>
<td>2.16 (1.19–3.92)</td>
<td>Referent</td>
</tr>
<tr>
<td>Adjudicated pulmonary embolism — no. (%)</td>
<td>9 (0.6)</td>
<td>24 (1.6)</td>
<td>3 (0.2)</td>
</tr>
<tr>
<td>Hazard ratio vs. TNF inhibitor (95% CI)</td>
<td>2.93 (0.79–10.83)</td>
<td>8.26 (2.49–27.43)</td>
<td>Referent</td>
</tr>
<tr>
<td>Adjudicated DVT — no. (%)</td>
<td>11 (0.8)</td>
<td>15 (1.0)</td>
<td>7 (0.5)</td>
</tr>
<tr>
<td>Hazard ratio vs. TNF inhibitor (95% CI)</td>
<td>1.54 (0.60–3.97)</td>
<td>2.21 (0.90–5.43)</td>
<td>Referent</td>
</tr>
<tr>
<td>Adjudicated VTE — no. (%)</td>
<td>17 (1.2)</td>
<td>34 (2.3)</td>
<td>10 (0.7)</td>
</tr>
<tr>
<td>Hazard ratio vs. TNF inhibitor (95% CI)</td>
<td>1.66 (0.76–3.63)</td>
<td>3.52 (1.74–7.12)</td>
<td>Referent</td>
</tr>
<tr>
<td>Adjudicated death from any cause — no. (%)</td>
<td>26 (1.8)</td>
<td>39 (2.7)</td>
<td>17 (1.2)</td>
</tr>
<tr>
<td>Hazard ratio vs. TNF inhibitor (95% CI)</td>
<td>1.49 (0.81–2.74)</td>
<td>2.37 (1.34–4.18)</td>
<td>Referent</td>
</tr>
</tbody>
</table>
What we know

Dermatologic disease x (e.g. sarcoidosis)

No treatment

JAK inhibitor x

Partial improvement

Greater improvement

Rheumatoid arthritis

No treatment

Tofacitinib + MTX

TNF-α in + MTX

Clinical Improvement

Clinical Improvement

No clinical improvement

Long-term outcome

Long-term outcome

Long-term outcome

What we don’t know

No improvement

Alternate treatment

Greater improvement

Clinical Improvement

Long-term outcome

Long-term outcome

Long-term outcome
Generalizability of this safety data has been questioned

<table>
<thead>
<tr>
<th></th>
<th>Rheum</th>
<th>Derm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient population</td>
<td>Older</td>
<td>Younger</td>
</tr>
<tr>
<td></td>
<td>More medical co-morbidities</td>
<td>Fewer or no co-morbidities</td>
</tr>
</tbody>
</table>
Why we can be optimistic this may be true, we also need to be careful

RCT of 717 patients with RA over 12 months on stable MTX
- Tofacitinib 5 mg bid
- Tofacitinib 10 mg bid
- Adalimumab 40 mg bid
- placebo

Study leading to:
- Approval of tofacitinib in RA
- Requirement for ORAL Surveillance study
There was no MACE or clotting signal with tofa in the initial trial.

<table>
<thead>
<tr>
<th>MedDRA System Organ Class</th>
<th>Placebo Followed by Tofacitinib, 5 mg (N = 56)</th>
<th>Placebo Followed by Tofacitinib, 10 mg (N = 52)</th>
<th>Tofacitinib, 5 mg (N = 204)</th>
<th>Tofacitinib, 10 mg (N = 201)</th>
<th>Adalimumab, 40 mg (N = 204)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac disorders</td>
<td>Atroventricular block complete</td>
<td>Acute myocardial infarction</td>
<td>Cardiac failure congestive, myocardial infarction</td>
<td>Acute myocardial infarction, cardiac arrest, myocardial infarction, myocardial ischemia</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Deep-vein thrombosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Greater need for basic and translational research to understand the mechanism of MACE and hypercoagulability seen in JAK inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Approval</th>
<th>+</th>
<th>+</th>
<th>+</th>
<th>-</th>
<th>Approved Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tofacitinib</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>RA, PSA, UC, JIA</td>
</tr>
<tr>
<td>Baricitinib</td>
<td></td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>RA, COVID-19, AD (EU)</td>
</tr>
<tr>
<td>Upadacitinib</td>
<td></td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>RA, AD</td>
</tr>
<tr>
<td>Abrocinib</td>
<td></td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>AD</td>
</tr>
<tr>
<td>Delgocitinib</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>AD (topical, Japan)</td>
</tr>
<tr>
<td>Filgotinib</td>
<td></td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>RA (EU, Japan)</td>
</tr>
<tr>
<td>Ruxolitinib</td>
<td></td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>GVHD, heme (topical AD, ? vitiligo)</td>
</tr>
<tr>
<td>Deucravacinib</td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>(trials – psoriasis)</td>
</tr>
<tr>
<td>Ritlecitinib</td>
<td></td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>(trials – AA)</td>
</tr>
</tbody>
</table>
Summary: safety and black boxed warnings

Boxed warnings: patient selection

- Serious infections
- Mortality
  - Age 65 and above
- Malignancies
  - Smokers – lung cancer
  - History of internal malignancy
- Major adverse cardiovascular events (MACE)
  - Smoker
  - History of MACE or risk factors for MACE
  - Aggressive treatment of lipids?
- Thrombosis
  - Smokers
  - History of DVT/PE
  - Screening for hypercoaguability?
  - Prophylactic anti-coagulation?

- We need to better understand mechanism of MACE and hypercoaguability so that we can understand how JAK inhibitor specificity might potentially mitigate this risk
Part 4: How selective are “selective” JAK inhibitors and does it matter?
JAK inhibitors have varying specificities and approvals

<table>
<thead>
<tr>
<th>Drug</th>
<th>JAK1</th>
<th>JAK2</th>
<th>JAK3</th>
<th>TYK2</th>
<th>Approved Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tofacitinib</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>RA, PSA, UC, JIA</td>
</tr>
<tr>
<td>Baricitinib</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>RA, COVID-19, AD (EU)</td>
</tr>
<tr>
<td>Upadacitinib</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>RA, AD</td>
</tr>
<tr>
<td>Abrocitinib</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>AD</td>
</tr>
<tr>
<td>Delgocitinib</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>AD (topical, Japan)</td>
</tr>
<tr>
<td>Filgotinib</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>RA (EU, Japan)</td>
</tr>
<tr>
<td>Ruxolitinib</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>GVHD, heme (topical AD, ? vitiligo)</td>
</tr>
<tr>
<td>Deucravacitinib</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>(trials – psoriasis)</td>
</tr>
<tr>
<td>Ritlecitinib</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>(trials – AA)</td>
</tr>
</tbody>
</table>
JAK specificity

• How is selectivity measured?
  • **Cell-free Assays**: Enzymatic assays with a portion of the kinase
    • Depends on assay conditions, e.g., concentration of ATP
    • The same results appear to not always be achieved (lab-to-lab or assay-to-assay variation)
  • **Cell-based Assays**: STAT activation (measurement of phosphorylation)
    • Depends on the stimulus (which cytokine, which STAT)
    • Depends on the cell type (e.g., effect in monocytes versus T cell)
    • Depends on environment (whole blood, tissue, cell culture)

• Clinical impact of isoform selectivity is dependent on:
  • Dose
  • Tissue type
  • Genetics of individual
  • Individual pharmacokinetics / metabolism
JAK selectivity and the implications for clinical inhibition of pharmacodynamic cytokine signalling by filgotinib, upadacitinib, tofacitinib and baricitinib

Paqui G Traves,1 Bernard Murray,2 Federico Campigotto,3 René Galien,4 Amy Meng,5 Julie A Di Paolo6
<table>
<thead>
<tr>
<th>Specificity</th>
<th>Ruxolitinib</th>
<th>Tofacitinib</th>
<th>Baricitinib</th>
<th>Upadacitinib</th>
<th>Filgotinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>JAK1/2</td>
<td>JAK1/2</td>
<td>JAK1/3 &gt; 2</td>
<td>JAK1/2</td>
<td>JAK1</td>
<td>JAK1</td>
</tr>
<tr>
<td>JAK1</td>
<td>3.3</td>
<td>3.2</td>
<td>5.9</td>
<td>43</td>
<td>10</td>
</tr>
<tr>
<td>JAK2</td>
<td>2.8</td>
<td>4.1</td>
<td>5.7</td>
<td>120</td>
<td>28</td>
</tr>
<tr>
<td>JAK3</td>
<td>428</td>
<td>1.6</td>
<td>&gt;400</td>
<td>2300</td>
<td>810</td>
</tr>
<tr>
<td>TYK2</td>
<td>19</td>
<td>34</td>
<td>53</td>
<td>4700</td>
<td>116</td>
</tr>
</tbody>
</table>

IC50 values reported in New Drug Application (NDA)
Lower: greater inhibition
Higher: lesser inhibition

IL-4 stimulation of monocytes in whole blood

D. JAK1/JAK3
- Fil (JAK1)
- Bari (JAK1/2)
- Tofa (JAK1/2/3)
- Upa (JAK1)

GM-CSF
- Fil (JAK1)
- Bari (JAK1/2)
- Tofa (JAK1/2/3)
- Upa (JAK1)

E. JAK2/JAK2
- Fil (JAK1)
- Bari (JAK1/2)
- Tofa (JAK1/2/3)
- Upa (JAK1)
Upshot: JAK specificity is super complicated!

• “The observed inhibition of JAKinibs on cytokine signaling was highly nuanced, and it was observed to be dependent on cytokine stimulus, STAT substrate, and cell type”

• Looking at adverse effects for different JAK inhibitors in clinical trials may provide more relevant information on specificity in vivo
  • Zoster (Type I IFNs – JAK1, JAK2, TYK2)
  • Thrombocytopenia (TPO – JAK2)
  • Anemia (EPO – JAK2)
  • Acne (mechanism), MACE (mechanism), Cancer (mechanism), etc.
New JAK inhdeuacravacitinib

- Review biological, AE data, indications
- Thoughts on why may be unique and which cytokines it hits, theoretical advantages
Ritlecitinib – jak3/tec

• In vitro, its 50% inhibitory concentration (IC50) for JAK3 is 33.1 nM, compared with > 10,000 nM for JAK1, JAK2, and TYK2.

• https://www.jaad.org/article/S0190-9622(21)00601-0/fulltext

• Review biological, AE data, indications

• Thoughts on why may be unique and which cytokines it hits, theoretical advantages
The cost of JAK inhibitors is not trivial

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA approved indications</th>
<th>Approximate price of 1 month prescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruxolitinib</td>
<td>Polycythemia vera, Myelofibrosis Graft-versus-host-disease</td>
<td>$15,000</td>
</tr>
<tr>
<td>Tofacitinib</td>
<td>Rheumatoid arthritis, Psoriatic arthritis Juvenile idiopathic arthritis Ulcerative colitis</td>
<td>$3350</td>
</tr>
<tr>
<td>Baricitinib</td>
<td>Rheumatoid arthritis EUA: Inpatient COVID-19 (with remdesivir)</td>
<td>$2375</td>
</tr>
<tr>
<td>Upadacitinib</td>
<td>Rheumatoid arthritis Atopic dermatitis</td>
<td>$7600</td>
</tr>
<tr>
<td>Abrocitinib</td>
<td>Atopic dermatitis</td>
<td>$2900</td>
</tr>
<tr>
<td><strong>Secukinumab</strong></td>
<td><strong>Psoriasis</strong></td>
<td><strong>$5500</strong></td>
</tr>
</tbody>
</table>
Summary

• JAK inhibitors will be an integral part of dermatology moving forward
• JAK inhibitors hold broad promise in the treatment of inflammatory skin diseases and this is being realized
• JAK inhibitors do have safety concerns but the mechanism and how different populations might be variably impacted needs to be better understood
• Selective JAK inhibitors are exciting but we need to remain judicious in evaluating the evidence
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• Pathology: Meaghan McGeary

• Yale Center for Clinical Investigation

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