

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

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Disclosures:

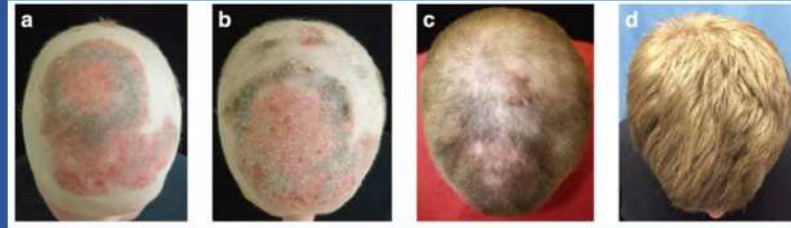
- Research support: Pfizer, Incyte, Advanced Cell Diagnostics/Bio-technie, AbbVie
- Consulting fees: Eli Lilly, Incyte, Pfizer, Twi Biotechnology
- Licensing fees: EMD/Millipore/Sigma
- I will discuss off label use of JAK inhibitors

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, 2988–2990; doi:10.1038/jid.2014.260; 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



BRIEF REPORT

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

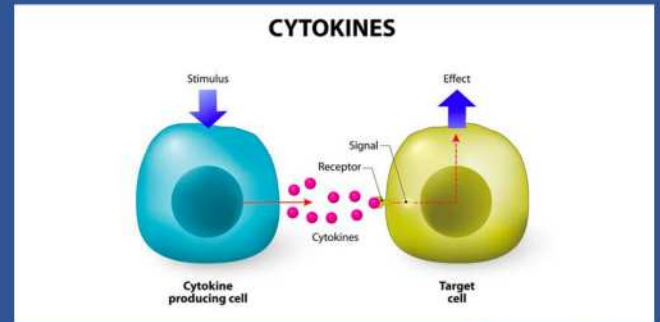
Overview of today's talk

- 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



BioAgilytix website

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 NOT signal via JAK-STAT
 - IL-1 β
 - TNF- α
 - IL-17
 - TGF- β
- 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

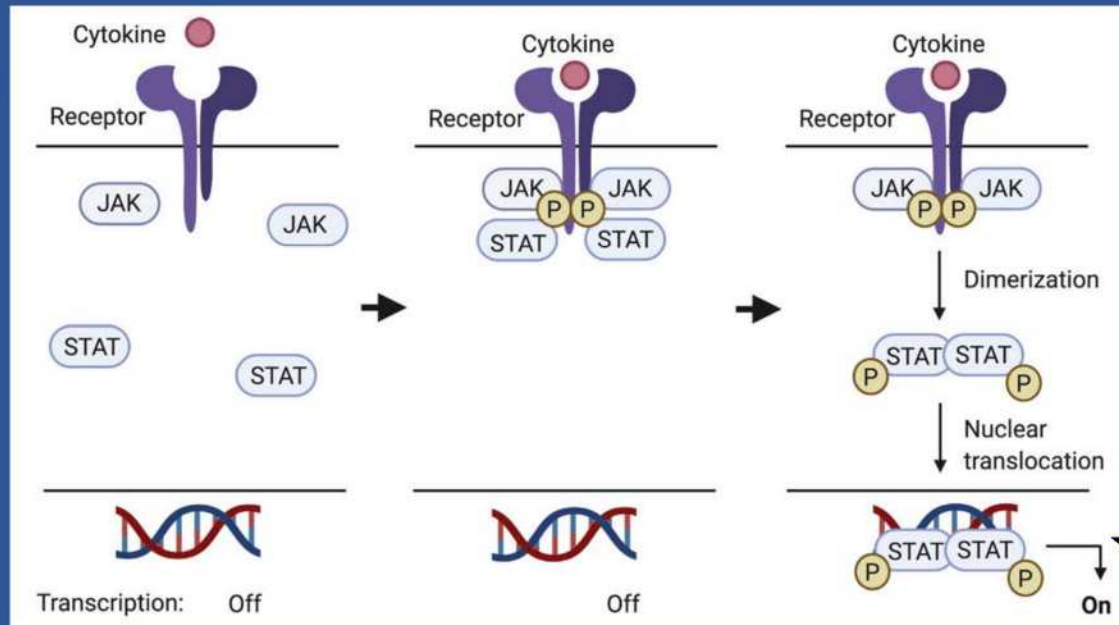
}	Th1 (Type 1)
}	Th2 (Type 2)
	Th17 (Type 3)
- Unexpected cytokines that signal via JAK-STAT!
 - Erythropoietin (EPO)
 - Thrombopoietin (TPO)
 - Growth hormone
 - Prolactin
 - Leptin

Signal

What is JAK-STAT signaling

JAK: Janus kinase

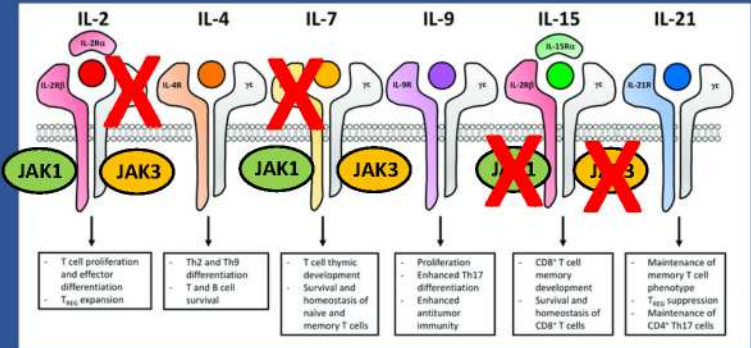
STAT: Signal Transducer and Activator of Transcription



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



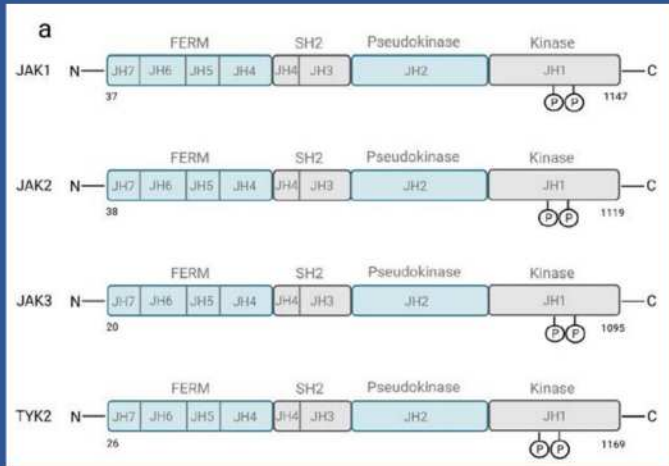
TYPES OF SEVERE COMBINED IMMUNODEFICIENCY (SCID)			
Disorder	Gene	Protein function and specific clinical features	Cells
<i>Defects in cytokine receptors and their signaling</i>			
X-linked SCID	IL2RG	Common γ chain (γ_c) of the receptors for IL-2, 4, 7, 9, 15, and 21	T ⁺ /B ⁻ /NK ⁻
JAK3 deficiency	JAK3	Tyrosine kinase with a role in signal transduction via the receptors for IL-2, 4, 7, 9, 15, and 21	T ⁺ /B ⁻ /NK ⁻
Interleukin-7 receptor deficiency	IL7R	α -chain of the IL-7 receptor; critical for development and differentiation of T cells; possible Omenn syndrome phenotype	T ⁺ /B ⁻ /NK ⁻

Bologna 4th Ed



JAK proteins are highly structurally similar

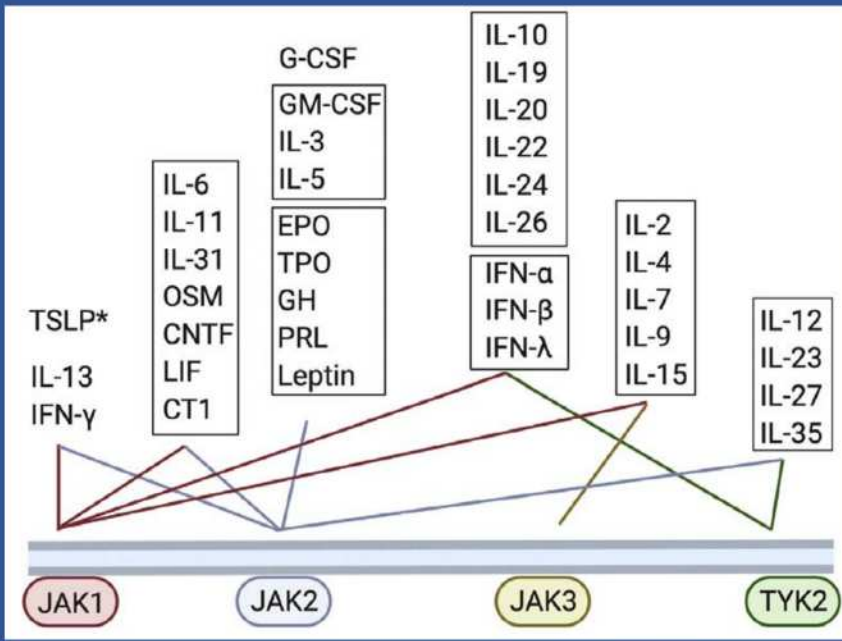
JAKs are tyrosine kinases
JAKs are very structurally similar!



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

	Knockout phenotype	Expression Patterns	Key Cytokines
JAK1	Lethal	Widely expressed	IFN- α/β , IFN- γ , IL-2, IL-4, IL-15, IL-6 family, IL-10 family
JAK2	Lethal (erythropoiesis)	Widely expressed	IFN- γ , IL-5, GM-CSF, TPO, EPO, G-CSF, GH
JAK3	SCID	Immune specific	γc (IL-2, IL-4, IL-7, IL-9, IL-15, IL-21)
TYK2 (JAK4)	Infections	Widely expressed	IFN- α/β , IL-12, IL-23

4 JAKs and 57 cytokines!



Damsky et al. J All Clin Immunol 2021

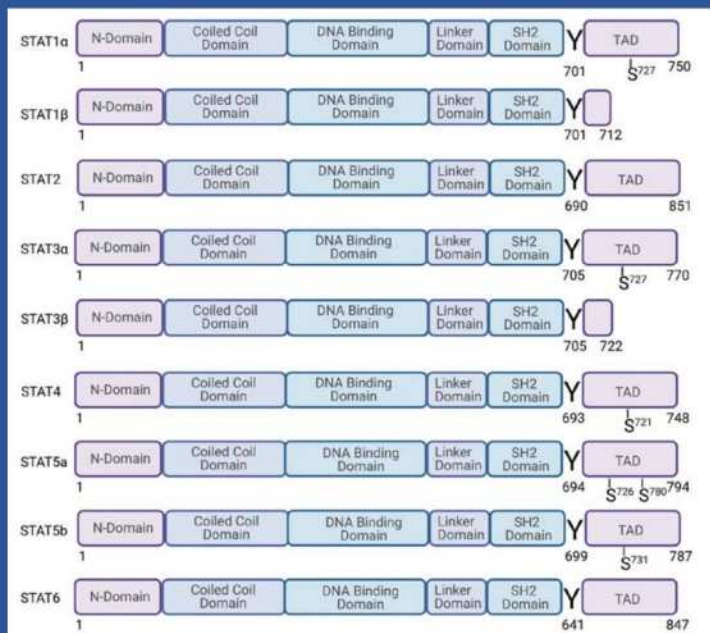
"Principles" of JAK inhibition:

- 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



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

	Genetic variation	Cytokines
STAT1	Susceptible to mycobacteria/virus (GOF STAT1: CMC)	Interferons (IFNs)
STAT2	Immunodeficiency	Type I IFNs (α/β)
STAT3	Lethal in mice (LOF STAT3: Hyper IgE syndrome aka Job)	IL-6 family
STAT4	Polymorphisms lupus, psoriasis	IL-12, IL-23, Type I IFNs (α/β)
STAT5A STAT5B	Autoimmunity, immunodeficiency, dwarfism	IL-2, EPO, TOP, GM-CSF, GH
STAT6	Polymorphisms atopic diseases	IL-4, IL-13

CMC: Chronic mucocutaneous candidiasis

GOF: gain of function

LOF: loss of function

Summary Part 1

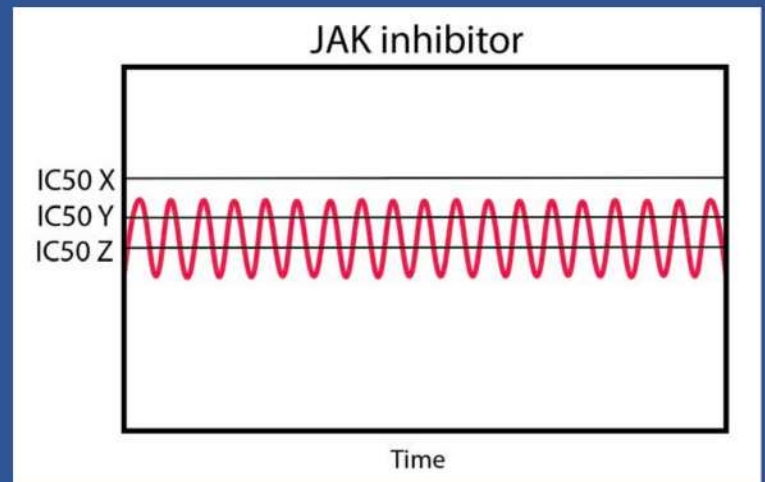
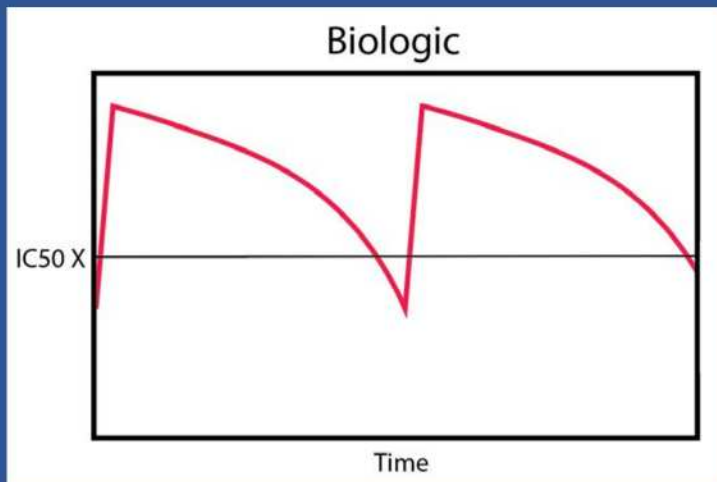
- Cytokines are secreted factors that regulate fundamental aspects of immunity (and other functions)
- Many (but not all) cytokines signal via the JAK-STAT pathway
- JAK-STAT signaling is important for regular immune function
- JAK-STAT signaling is overactivated in auto-immune and inflammatory diseases 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!

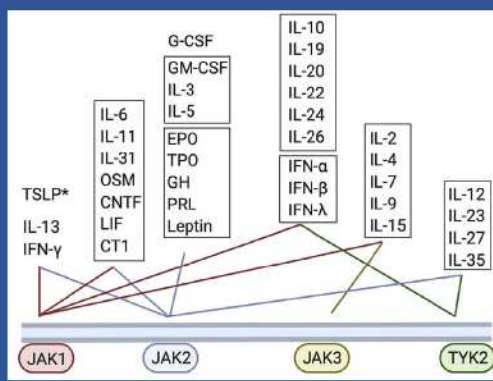
Doses of JAK inhibitors used to treat autoimmunity significantly lower than used in other settings explored during development

e.g., tofacitinib 5 mg bid – autoimmunity

vs. tofacitinib 30 mg bid – prevent organ transplant rejection

What JAK inhibitors are on the market now?

JAK inhibitors have varying specificities and approvals



Drug

Approved Indications

Drug	JAK1	JAK2	JAK3	TYK2	Approved Indications
Tofacitinib	+	+	+	-	RA, PSA, UC, JIA
Baricitinib	+	+	-	-	RA, COVID-19, AD (EU)
Upadacitinib	+	-	-	-	RA, AD
Abrocitinib	+	-	-	-	AD
Delgocitinib	+	+	+	+	AD (topical, Japan)
Filgotinib	+	-	-	-	RA (EU, Japan)
Ruxolitinib	+	+	-	-	GVHD, heme (topical AD, ? vitiligo)
Deucravacitinib	-	-	-	+	(trials – psoriasis)
Ritlecitinib	-	-	+	-	(trials – AA)

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:

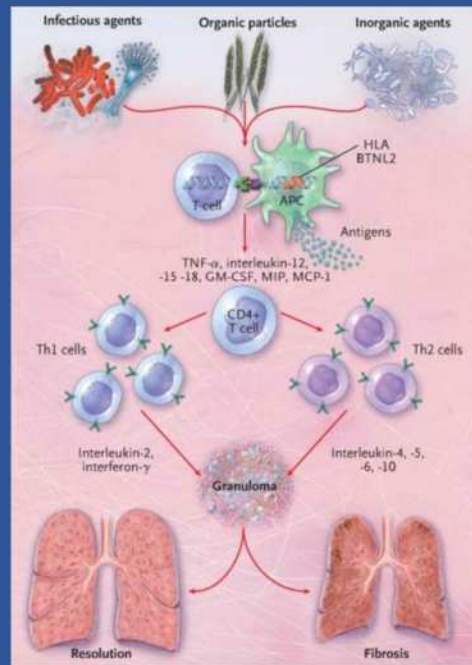
MIP (CCL3)
MCP1 (CCL2)



Bologna 4th ed



Bologna 4th ed



Iannuzzi et al N Engl J Med 2007

See also: Drent et al. N Engl J Med 2021

Would a JAK inhibitor work to treat sarcoidosis?

48-year-old woman
with long-standing
sarcoidosis who had
failed a number of
therapies previously

BRIEF REPORT

Tofacitinib Treatment and Molecular Analysis of Cutaneous Sarcoidosis

William Damsky, M.D., Ph.D., Durga Thakral, M.Phil., M.S.,
Nkiruka Emeagwali, M.D., Ph.D., Anjela Galan, M.D., and Brett King, M.D., Ph.D.

A Skin Disease before and during Treatment

Before Treatment

During Treatment

Before Treatment

During Treatment



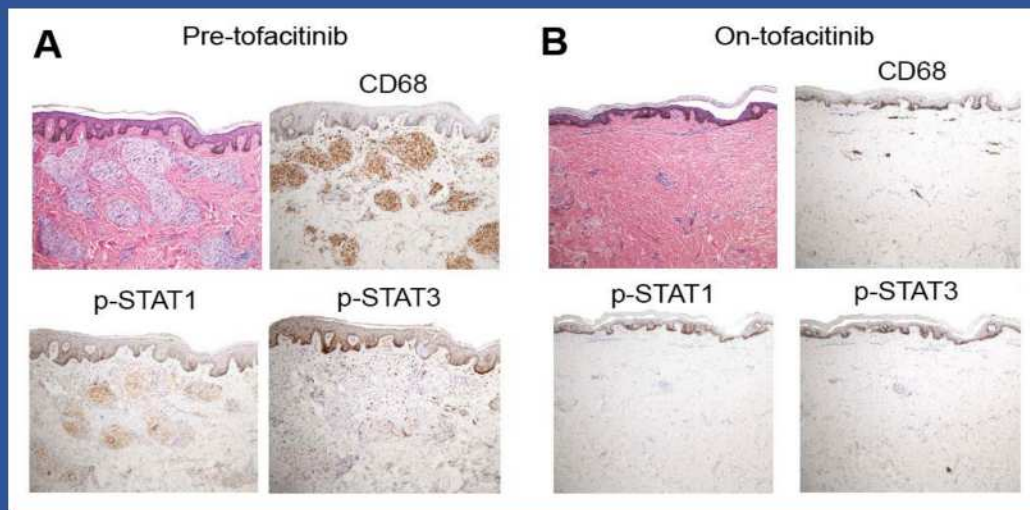
No treatment

tofacitinib 5 mg bid

No treatment

tofacitinib 5 mg bid

Histologic resolution of granulomas with tofacitinib



p = 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

Drug	JAKs	Dose	n	Δ Cutaneous?	Δ Systemic?	Disease duration	Fitzpatrick type	Sex	Country	Reference
Oral JAK inhibition										
Tofacitinib	JAK1/2/3	5 mg twice daily	1	CR	N/A	8 y	II	F	United States	Damsky et al ⁴
Tofacitinib	JAK1/2/3	5 mg twice daily	3	CR (3)	N/A	6-25 y	VI	2 F, 1 M	United States	Damsky et al ⁵
Tofacitinib	JAK1/2/3	5-10 mg twice daily	1	CR	CR	21 y	I	F	United States	Damsky et al ⁵
Tofacitinib	JAK1/2/3	2.5-16 mg daily	5	CR/NCR (3), PR (2)	PR (3), N/A (2)	Not reported	White	F	Australia	Kerkemeyer et al ⁶
Tofacitinib	JAK1/2/3	5 mg twice daily	5	N/A	PR (3), N/A (2)	1-5 y	4 Caucasian, 1 African American	4 M, 1 F	United States	Friedman et al ⁷
Ruxolitinib	JAK1/2	5 mg twice daily	1	CR	NCR	18 y	European ancestry	F	France	Rotenberg et al ¹⁰
Ruxolitinib	JAK1/2	10 mg twice daily	1	CR	PR	1 y	VI	F	United States	Wei et al ¹¹
Ruxolitinib	JAK1/2	20 mg daily	1	N/A	CR	5 y	Not reported	F	France	Levrault et al ¹²
Baricitinib	JAK1/2	4 mg daily	1	N/A	CR	10 wk	Not reported	F	Brazil	Scheinberg et al ¹³
Topical JAK inhibition										
Tofacitinib	JAK1/2/3	2% ointment twice daily	1	PR	N/A	5 y	II	F	United States	Singh et al ¹⁴
Tofacitinib	JAK1/2/3	2% ointment twice daily	1	PR	N/A	9 y	VI	M	United States	Alam et al ¹⁵

CR, Complete response; F, female; JAK, Janus kinase; M, male; N/A, not applicable; NCR, near complete response; PR, partial response.

Talty et al. 2021 JAAD Case Rep

CASE REPORT

Treatment of cutaneous sarcoidosis with tofacitinib: A case report and review of evidence for Janus kinase inhibition in sarcoidosis

Ronan Talty, BS,^{1,2} William Damsky, MD, PhD,^{1,2} and Brett King, MD, PhD²
New Haven, Connecticut

CASE REPORT

Resolution of cutaneous sarcoidosis after Janus kinase inhibitor therapy for concomitant polycythemia vera

Jenny J. Wei, BS,¹ Lisa R. Kallenbach, MD, MPA,² Maryl Kreider, MD,² Thomas H. Leung, MD, PhD,^{1,2} and Misha Rosenbach, MD²
Philadelphia, Pennsylvania

Janus kinase inhibition induces disease remission in cutaneous sarcoidosis and granuloma annulare

William Damsky, MD, PhD,¹ Durga Thakral, PhD,² Meaghan K. McGeary, BA,² Jonathan Leventhal, MD,² Anjela Galan, MD,² and Brett King, MD, PhD²
New Haven, Connecticut

Inhibition of type 1 immunity with tofacitinib induces marked improvement in longstanding sarcoidosis

William Damsky MD, PhD^{1,2,*}, Alice Wang BS¹, Daniel J. Kim PhD¹, Bryan D. Young MD, PhD³, Katelyn Singh BS¹, Michael J. Murphy BS¹, Joseph Daccache BA¹, Abigale Clark BA⁴, Ruveyda Ayasun MD, PhD⁵, Changwan Ryu MD PhD⁶, Meaghan K. McGeary BA², Ian D. Odell MD, PhD^{1,7}, Ramesh Fazzzone-Chettiar BS³, Darko Pucar MD, PhD⁸, Robert Homer MD, PhD², Mridu Gulati MD⁶, Edward J. Miller MD, PhD³, Marcus Bosenberg MD, PhD^{1,2,7}, Richard A. Flavell PhD^{7,9}, Brett King MD, PhD^{1,*}

Open label trial in 10 patients with sarcoidosis involving skin

- tofacitinib 5 mg twice daily for 6 months
- long-standing severe disease

Skin:

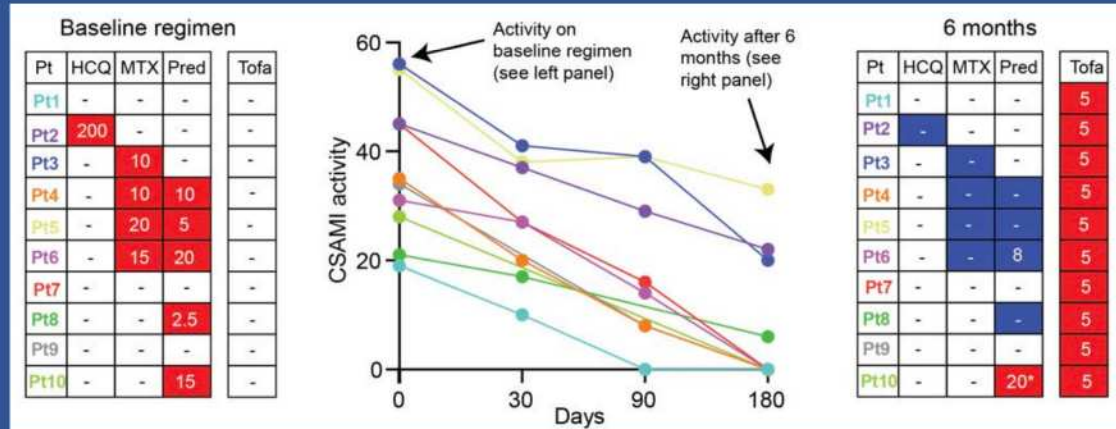
- 6 complete responses in skin
- 4 partial responses in skin

Internal:

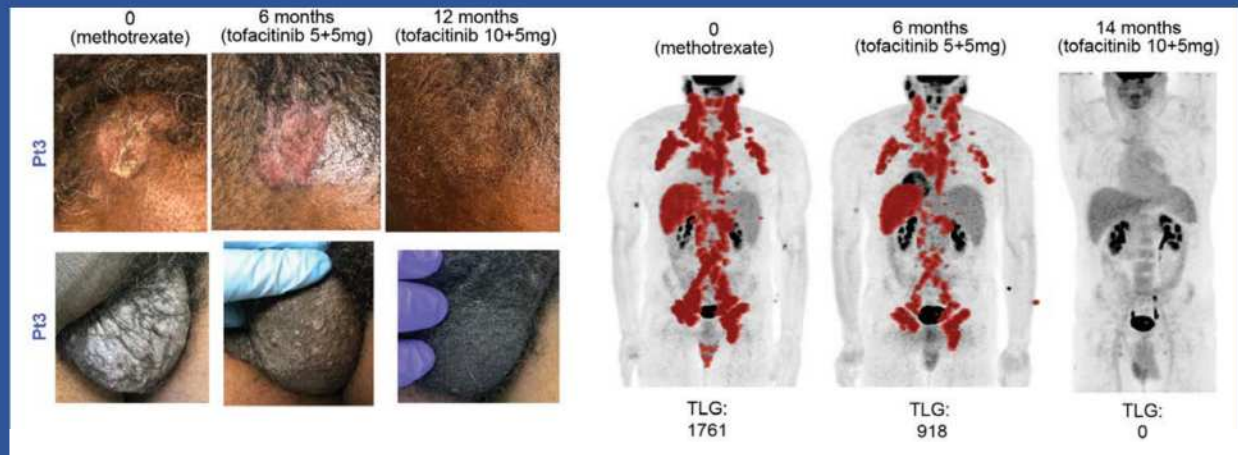
- Most patients improved

Patients generally able to reduce or discontinue baseline immunosuppression (methotrexate, prednisone)

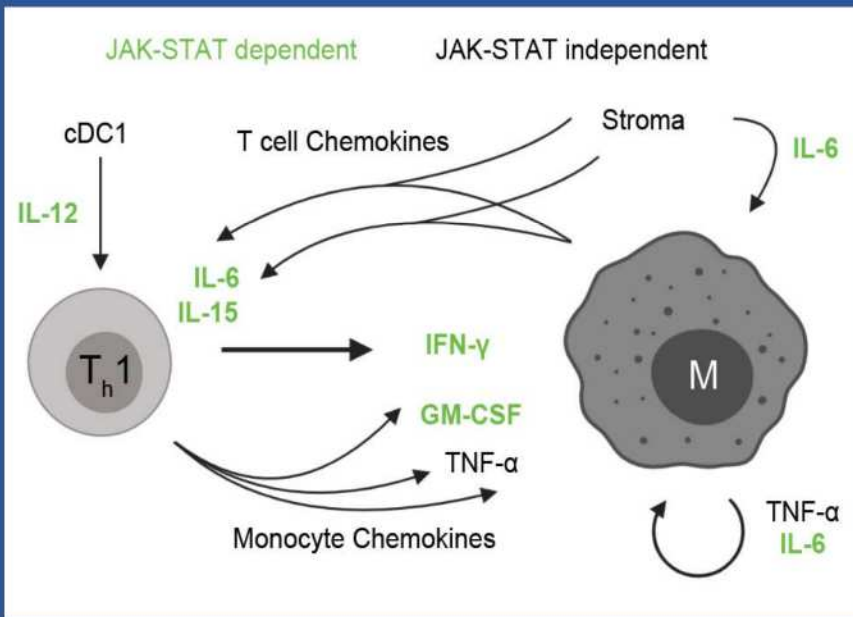
No significant AEs



Damsky et al Nature Communications in press (Preprint on Medrxiv)



Why did JAK inhibition work in sarcoidosis?



Primary mechanism:

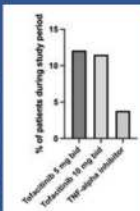
- Inhibition of IFN- γ (JAK1/2)

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- γ , 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- γ (marker: risk of zoster reactivation)

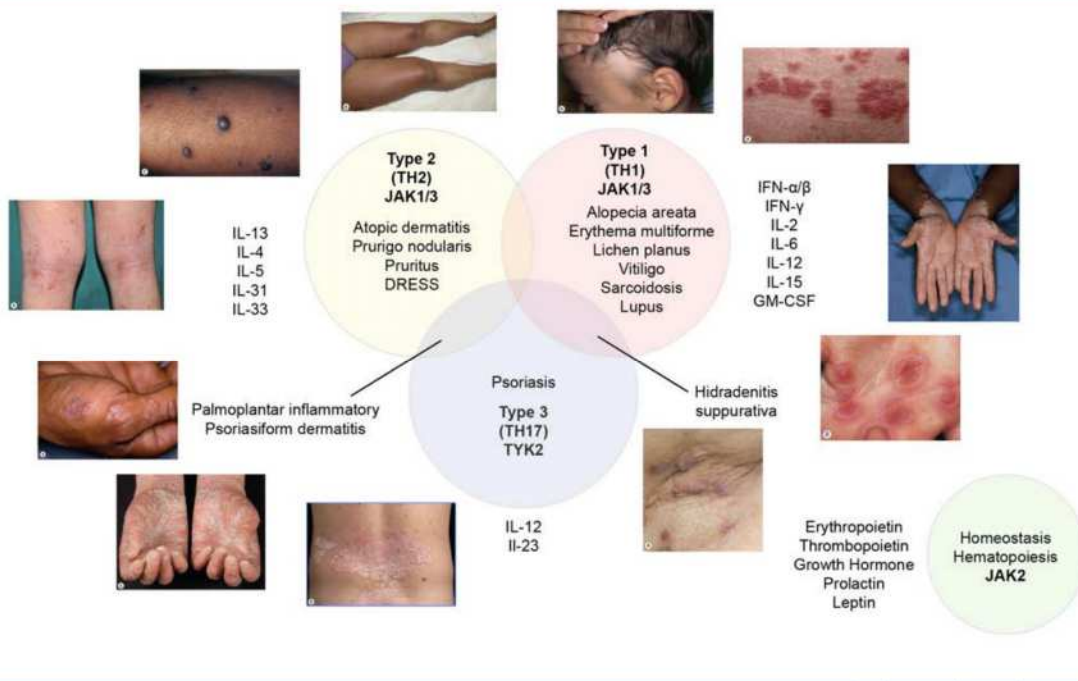


JAK inhibitors can treat “classic” and “non-classic” disease

- “Psoriasiform dermatitis” – both Th2 and Th 17 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



Clinical Images from Bologna 4th Ed

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)

Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis

N England J Med 2022; Ytterberg et al.

- 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- α 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 ≥ 1.8 (tofacitinib both groups combined vs TNF- α inhibitor)
- 333 sites in 20 countries (March 2014 – July 2020)
- Median follow-up: 4 years

Patients

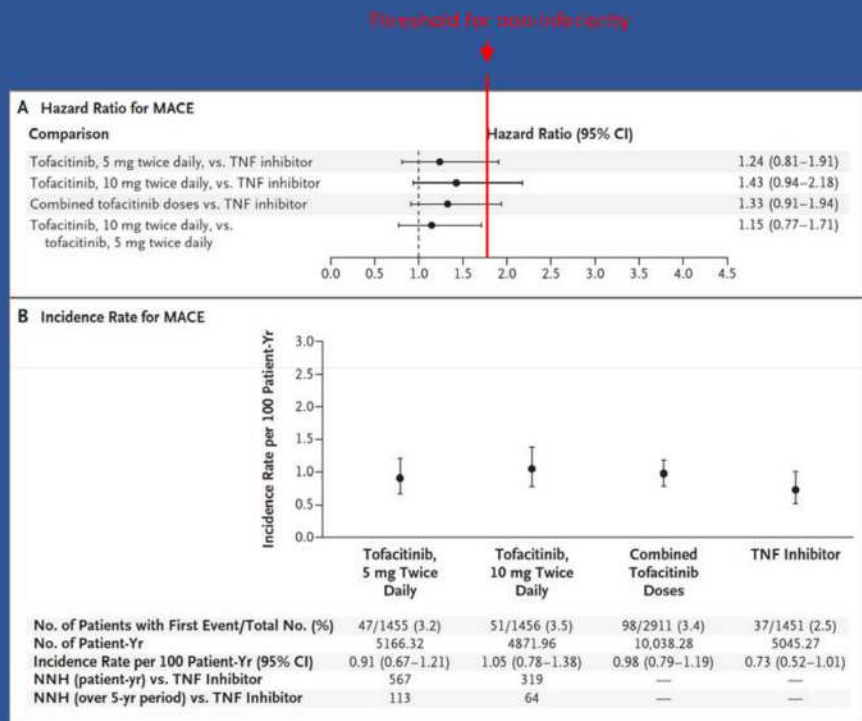
- Active RA despite methotrexate
 - Background methotrexate was continued (unless modification was clinically indicated)
- 50 years or older with at least one additional CV risk factor
 - Current cigarette smoker
 - Hypertension
 - HDL < 40 mg/dL
 - Diabetes mellitus
 - Family history of premature coronary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

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Safety Analysis Population).^a

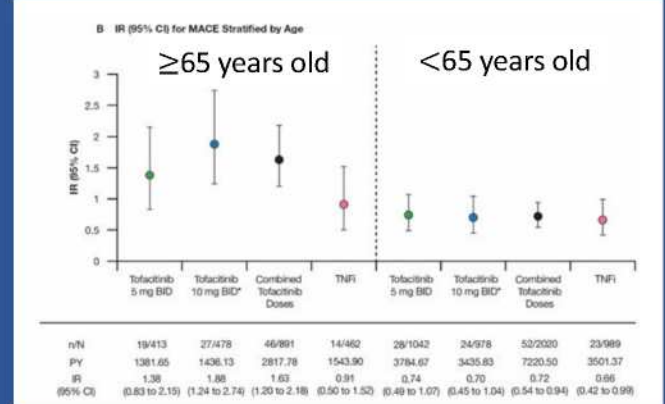
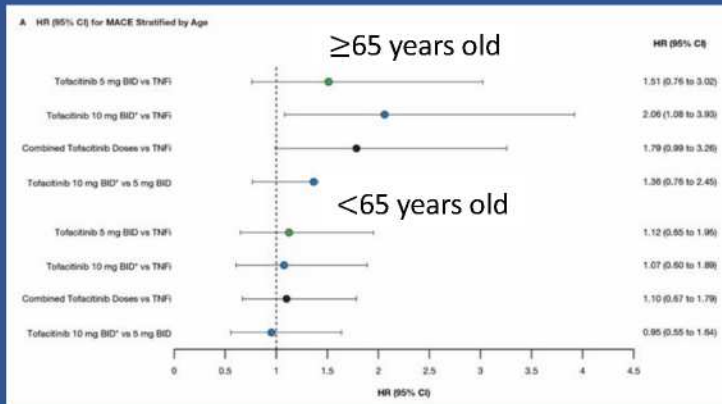
Characteristic	Tofacitinib, 5 mg Twice Daily (N = 1455)	Tofacitinib, 10 mg Twice Daily (N = 1456) [†]	TNF Inhibitor (N = 1451)	Total (N = 4362)
Age				
Mean — yr	60.8 ± 6.8	61.4 ± 7.1	61.3 ± 7.5	61.2 ± 7.1
≥65 yr — no. (%)	413 (28.4)	478 (32.8)	462 (31.8)	1353 (31.0)
Female sex — no. (%)	1169 (80.3)	1124 (77.2)	1117 (77.0)	3410 (78.2)
Race — no. (%) [‡]				
White	1128 (77.5)	1126 (77.3)	1099 (75.7)	3353 (76.9)
Black	63 (4.3)	65 (4.5)	83 (5.7)	211 (4.8)
Asian	65 (4.5)	56 (3.8)	55 (3.8)	176 (4.0)
Other	199 (13.7)	209 (14.4)	214 (14.7)	622 (14.3)
Smoking status — no. (%)				
Never smoked	735 (50.5)	752 (51.6)	772 (53.2)	2259 (51.8)
Ever smoked	720 (49.5)	704 (48.4)	679 (46.8)	2103 (48.2)
History of hypertension — no. (%)	955 (65.6)	954 (65.5)	969 (66.8)	2878 (66.0)
History of diabetes mellitus — no. (%)	243 (16.7)	261 (17.9)	255 (17.6)	759 (17.4)
History of venous thromboembolism — no. (%) [§]	19 (1.3)	33 (2.3)	27 (1.9)	79 (1.8)
History of extraarticular disease — no. (%) [¶]	532 (36.6)	521 (35.8)	552 (38.0)	1605 (36.8)
History of coronary heart disease — no. (%)	161 (11.1)	172 (11.8)	164 (11.3)	497 (11.4)
Family history of coronary heart disease — no. (%)				
First-degree male relative <55 yr of age	154 (10.6)	132 (9.1)	151 (10.4)	437 (10.0)
First-degree female relative <65 yr of age	115 (7.9)	107 (7.3)	100 (6.9)	322 (7.4)
Fasting HDL cholesterol <40 mg/dl — no. (%)	172 (11.8)	195 (13.4)	173 (11.9)	540 (12.4)

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

MACE: unanswered questions

Mechanism: We don't really know

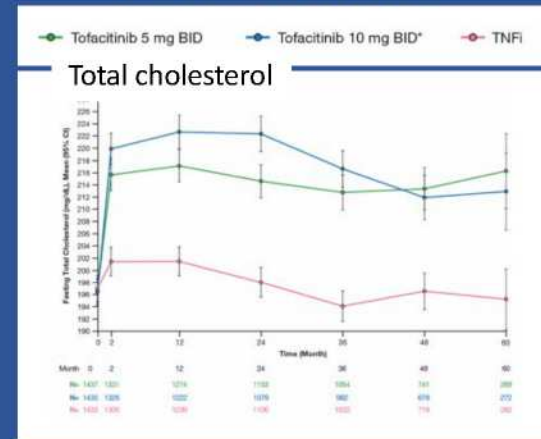
- Lipid dependent?
- Direct effect if JAK inhibitor?
- Multifactorial?

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

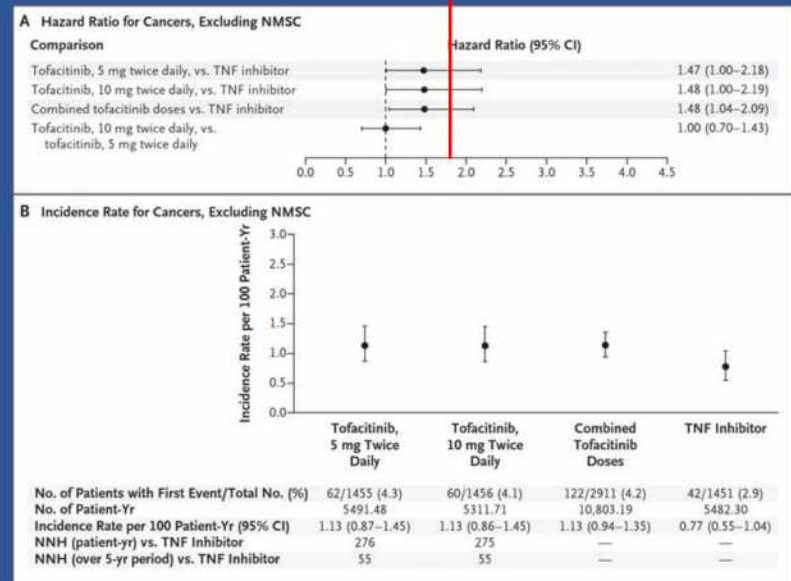
Does underlying disease state matter: we don't really know

JAKi increases cholesterol

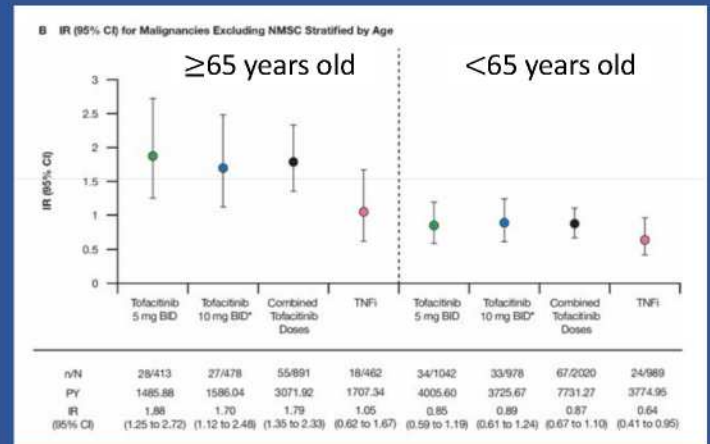
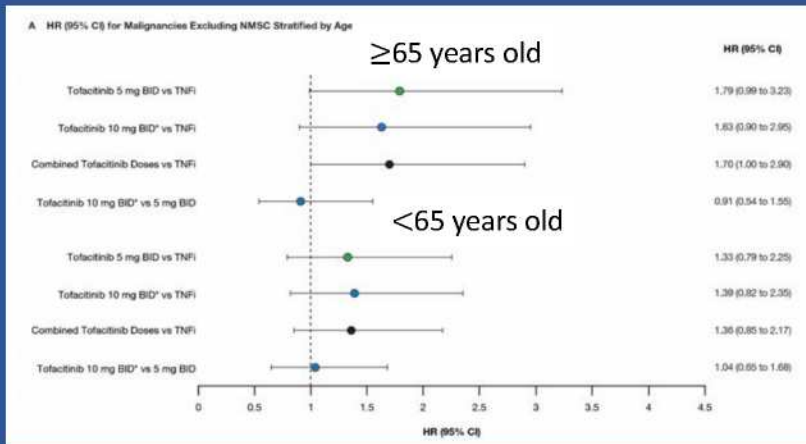


Cancer

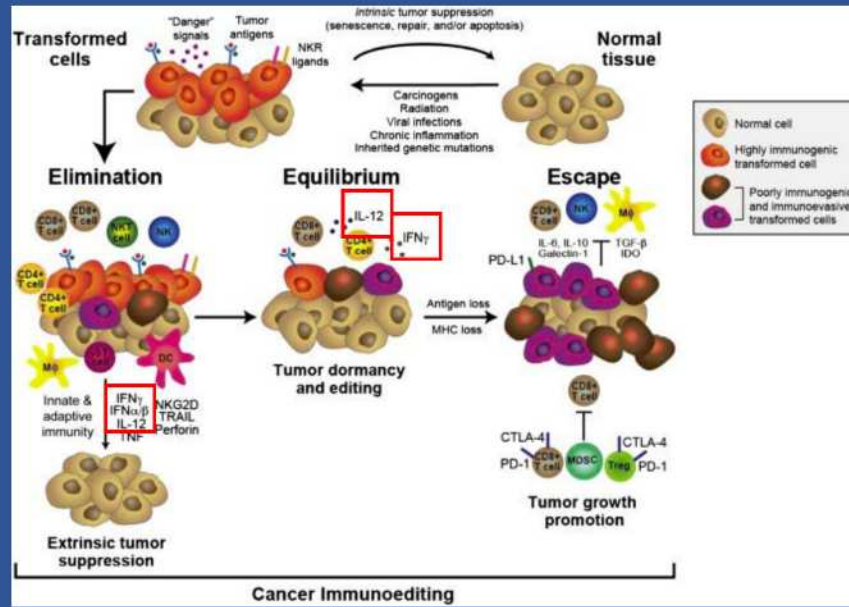
- Any cancer (excluding non-melanoma skin cancer)
- Cumulative estimated probability over 5.5 years:
 - Tofacitinib combined: 6.1%
 - TNF- α : 3.8% of patients
- HR: 1.48 (1.04-2.09)
- Most commonly lung cancer
- (NMSC also higher in the tofacitinib groups)



MACE (Stratified by age)



Cancer Mechanism: decreased tumor immunosurveillance?

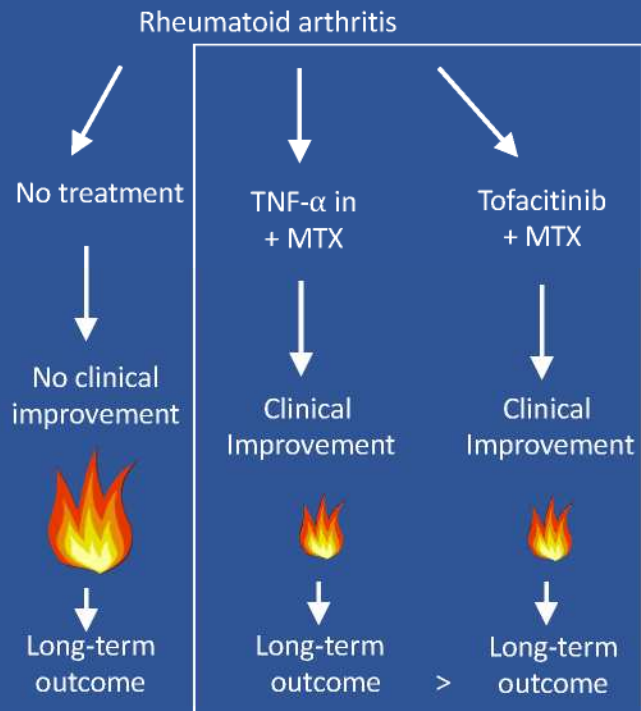


Lussier et al Elsevier Sci Tech connect 2016

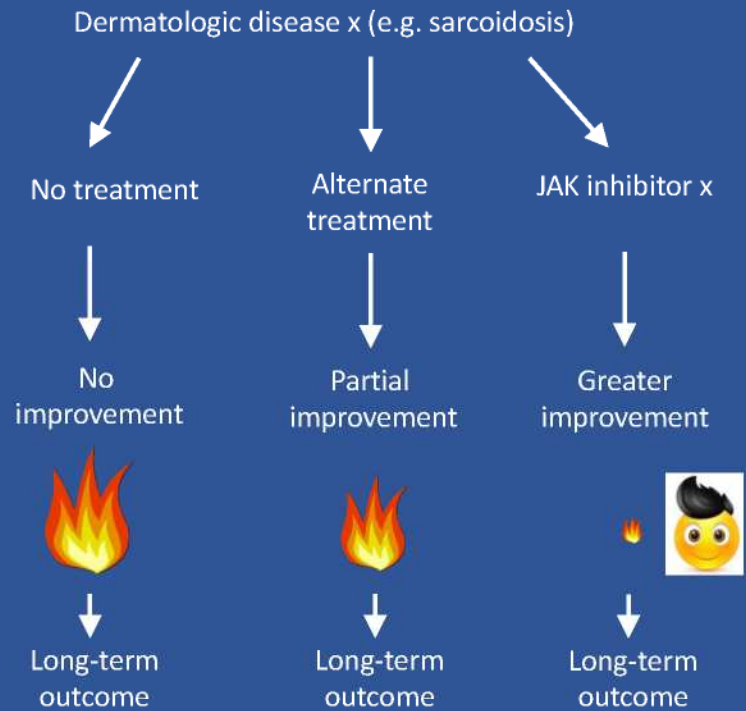
Other AE

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

What we know



What we don't know



Generalizability of this safety data has been questioned

	Rheum	Derm
Patient population	Older More medical co-morbidities	Younger Fewer or no co-morbidities

Why we can be optimistic this may be true, we also need to be careful



Study leading to:

- Approval of tofacitinib in RA
- Requirement for ORAL Surveillance study

- 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

There was no MACE or clotting signal with tofa in the initial trial

Table 3. Serious Adverse and Infection Events Over the Course of 12 Months, According to Treatment Sequence.*

MedDRA System Organ Class	Placebo Followed by Tofacitinib, 5 mg (N = 56)	Placebo Followed by Tofacitinib, 10 mg (N = 52)	Tofacitinib, 5 mg (N = 204)	Tofacitinib, 10 mg (N = 201)	Adalimumab, 40 mg (N = 204)
Cardiac disorders		Atrioventricular block complete	Acute myocardial infarction	Cardiac failure congestive, myo- cardial infarction	Acute myocardial infarction, cardiac arrest, myocardial ischemia
Vascular disorders				Deep-vein thrombosis	

Things will get complicated quickly!

Greater need for basic and translational research to understand the mechanism of MACE and hypercoagulability seen in JAK inhibitors

Drug					Approved Indications
Tofacitinib	+	+	+	-	RA, PSA, UC, JIA
Baricitinib	+	+	-	-	RA, COVID-19, AD (EU)
Upadacitinib	+	-	-	-	RA, AD
Abrocitinib	+	-	-	-	AD
Delgocitinib	+	+	+	+	AD (topical, Japan)
Filgotinib	+	-	-	-	RA (EU, Japan)
Ruxolitinib	+	+	-	-	GVHD, heme (topical AD, ? vitiligo)
Deucravacitinib	-	-	-	+	(trials – psoriasis)
Ritlecitinib	-	-	+	-	(trials – AA)

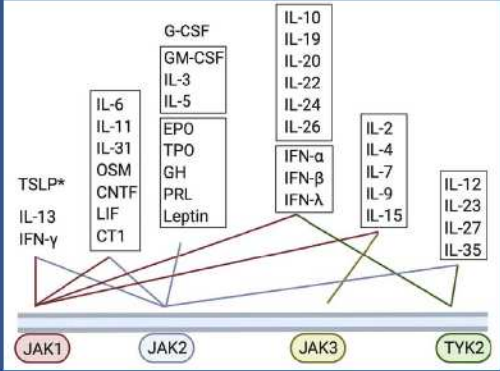
Summary: safety and black boxed warnings

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 hypercoagulability?*
 - *Prophylactic anti-coagulation?*
- We need to better understand mechanism of MACE and hypercoagulability 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



Drug					Approved Indications
Tofacitinib	+	+	+	-	RA, PSA, UC, JIA
Baricitinib	+	+	-	-	RA, COVID-19, AD (EU)
Upadacitinib	+	-	-	-	RA, AD
Abrocitinib	+	-	-	-	AD
Delgocitinib	+	+	+	+	AD (topical, Japan)
Filgotinib	+	-	-	-	RA (EU, Japan)
Ruxolitinib	+	+	-	-	GVHD, heme (topical AD, ? vitiligo)
Deucravacitinib	-	-	-	+	(trials – psoriasis)
Ritlecitinib	-	-	+	-	(trials – AA)

JAK specificity

- How is selectivity measured?
 - Cell-free Assays: Enzymatic assays with a portion of the kinase
 - Depends on assay conditions, eg 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 of environment (whole blood, tissue, cell culture)
- Clinical impact of isoform selectivity is dependent on:
 - Dose
 - Tissue type
 - Genetics of individual
 - Individual pharmacokinetics / metabolism



Rheumatoid arthritis



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JAK selectivity and the implications for clinical inhibition of pharmacodynamic cytokine signalling by filgotinib, upadacitinib, tofacitinib and baricitinib

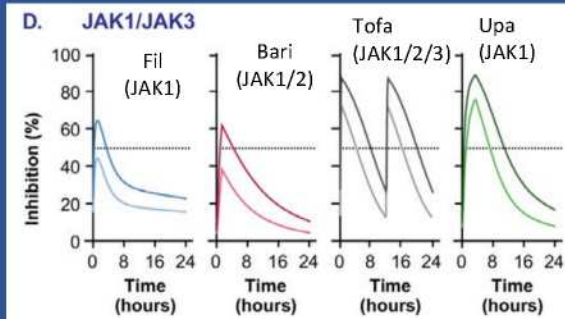
Paqui G Traves,¹ Bernard Murray,² Federico Campigotto,³ René Galien,⁴ Amy Meng,⁵ Julie A Di Paolo⁶

	Ruxolitinib	Tofacitinib	Baricitinib	Upadacitinib	Filgotinib
Specificity	JAK1/2	JAK1/3 > 2	JAK1/2	JAK1	JAK1
JAK1	3.3	3.2	5.9	43	10
JAK2	2.8	4.1	5.7	120	28
JAK3	428	1.6	>400	2300	810
TYK2	19	34	53	4700	116

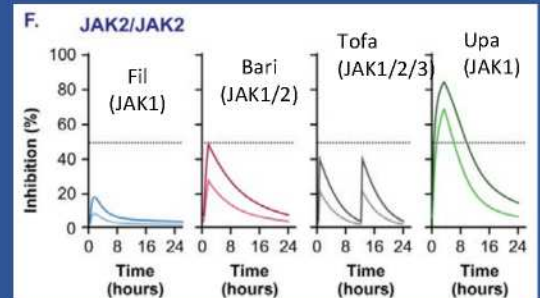
IC50 values reported in New Drug Application (NDA)
Lower: greater inhibition Higher: lesser inhibition

IL-4 stimulation of monocytes in whole blood

IL-4
↓
JAK1/3
↓
STAT6
↓
effect



GM-CSF
↓
JAK2/2
↓
STAT5
↓
effect



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 inhdeucravacitinib

- 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](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

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

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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The Dermatology Foundation
has supported & advanced my research
– and patient care.