A SPECIAL SUPPLEMENT OF CANADIAN DERMATOLOGY TODAY

AN OVERVIEW OF JANUS KINASE (JAK) INHIBITORS

ABOUT THE AUTHOR

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WHAT TO KNOW ABOUT JAK INHIBITORS

Background:
Atopic dermatitis (AD) is a common inflammatory skin disorder characterized by barrier defect and immune dysfunction.[1] Patients often suffer from severe itch that has a major impact on quality of life. Over 90% of patients report daily itch and over 50% report an impact on sleep patterns.[2] There are numerous related co-morbidities associated with AD including attention-deficit/hyperactivity disorder, depression, anxiety, insomnia, and poor school performance.[3]

Part of a successful treatment approach for AD includes patient education and the liberal use of moisturizers (those with ceramides). Additionally, topical corticosteroids and/or non-steroidal agents (such as topical calcineurin inhibitors and phosphodiesterase-4 inhibitors) are mainstays of treatment.[1] For many years, severe atopic dermatitis was treated with the off-label use of phototherapy, methotrexate, cyclosporine, mycophenolate, or azathioprine. The first Health Canada-approved systemic treatment for atopic dermatitis, dupilumab, was approved in 2017. Dupilumab is a recombinant human IgG4 monoclonal antibody that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling by specifically binding to the IL-4Rα subunit shared by the IL-4 and IL-13 receptor complexes.[4] Although efficacious and generally well-tolerated, dupilumab can have a slow onset of action and a variable clinical response in some patients. Another monoclonal antibody, tralokinumab, which is a fully human IgG4 monoclonal antibody that specifically binds to the type 2 cytokine IL-13 and inhibits its interaction with the IL-13 receptors, IL-13Rα1 and IL-13Rα2, was approved by Health Canada in October 2021.[5]

JAK-STAT Pathway in AD Pathogenesis:
There have been several oral novel small molecules in development for atopic dermatitis that target the Janus kinase (JAK) signal transducer and activator of transcription (STAT) pathway.[6] The JAK-STAT pathway intersects with key cytokines involved in both Th2 skin disease including IL-4, IL-13, IL-31, and thymic stromal lymphopoietin (TSLP). It can also target Th1, Th22 pathways allowing activity across diverse immune pathways and heterogenous disease presentations, including psoriasiform dermatitis, thereby potentially helping with overlap disease phenotypes. Different JAK inhibitors have variable selectivity (JAK1-3, and tyrosine kinase 2 [TYK2]), and several agents have now been thoroughly studied across clinical trials.

JAK Inhibitors for Atopic Dermatitis:
Upadacitinib:
Upadacitinib (RINVOQ®) is the first Health Canada approved oral JAK1 selective inhibitor indicated for the treatment of refractory moderate-to-severe atopic dermatitis in individuals aged 12 years or older who are not adequately controlled with systemic therapies.[7] It is available in 15 mg or 30 mg

doses with a recommended starting dose of 15 mg once daily. Dose titration may be considered if an adequate response (e.g., Eczema Area and Severity Index [EASI 75]) is not achieved. The recommended dose of RINVOQ is 15 mg once daily for adolescents weighing at least 40 kg. RINVOQ has not been studied in adolescents weighing less than 40 kg.[7] In the dual pivotal phase 3 clinical trials (Measure Up 1 & 2), a total of 1,683 subjects were assigned to oral upadacitinib 15 mg daily, upadacitinib 30 mg daily, or placebo. Taking the Measure Up 1 study as an example, patients in both intervention groups met the coprimary endpoint of EASI-75 at week 16 (70% & 80%, respectively) compared to 16% for placebo (P<0.0001) (**Figure 1A**).[8] The studies also achieved their co-primary endpoint of validated Investigator Global Assessment for AD (vIGA-AD) response i.e., score of 0 [clear] or 1 [almost clear] with ≥2 grades of reduction from baseline. (**Figure 1B**) Importantly, significant changes in EASI-75 and vIGA-AD 0/1 responders were seen as early as after 1 week of treatment. Efficacy at week 16 was maintained through week 52, with EASI-75 and 90 response achieved by 80.6% and 62.0% of patients continuing the 15-mg dose and 84.6% and 71.8% of patients continuing the 30-mg dose, respectively (pooled results from Measure Up 1 [depicted in **Figure 1C and D**] and Measure Up 2).[9] The clinical efficacy of upadacitinib remained very consistent in the AD Up trial, compared both doses were compared to placebo on a background of topical corticosteroids (TCS).[10]

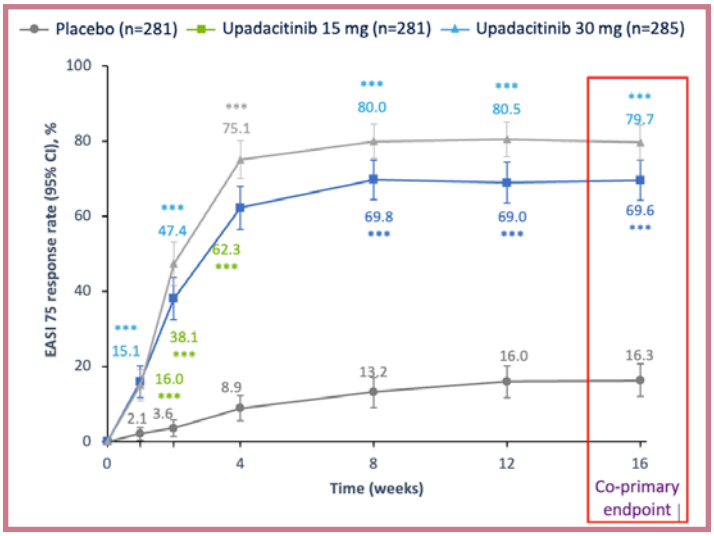


Figure 1A. EASI-75 response rates at Week 16; adapted from Guttman-Yassky E, et al. Lancet 2021;397:2151–68;Guttman-Yassky E, et al. EADV 2020 abstract [D3T03.4B]

***p≤0.001 vs placebo; p values are multiplicity controlled only at Weeks 2 and 16; p values are nominal at all other time points
[a]Based on ITT population, NRI-C
CI, confidence interval; EASI 75, ≥75% improvement in Eczema Area and Severity Index; ITT, intent-to-treat for the main study; NRI-C, non-responder imputation incorporating Multiple Imputation to handle missing data due to coronavirus disease 2019

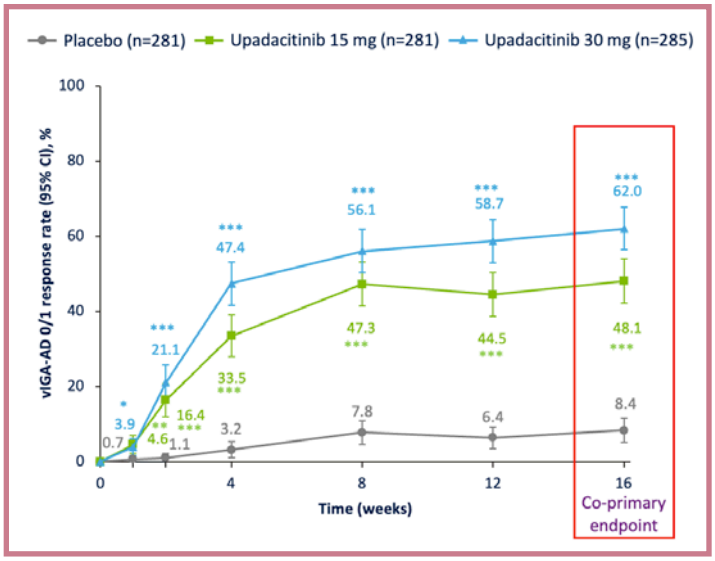


Figure 1B. vIGA-AD 0/1a response rates at Week 16; adapted from Guttman-Yassky E, et al. Lancet 2021;397:2151–68;Guttman-Yassky E, et al. EADV 2020 abstract [D3T03.4B]

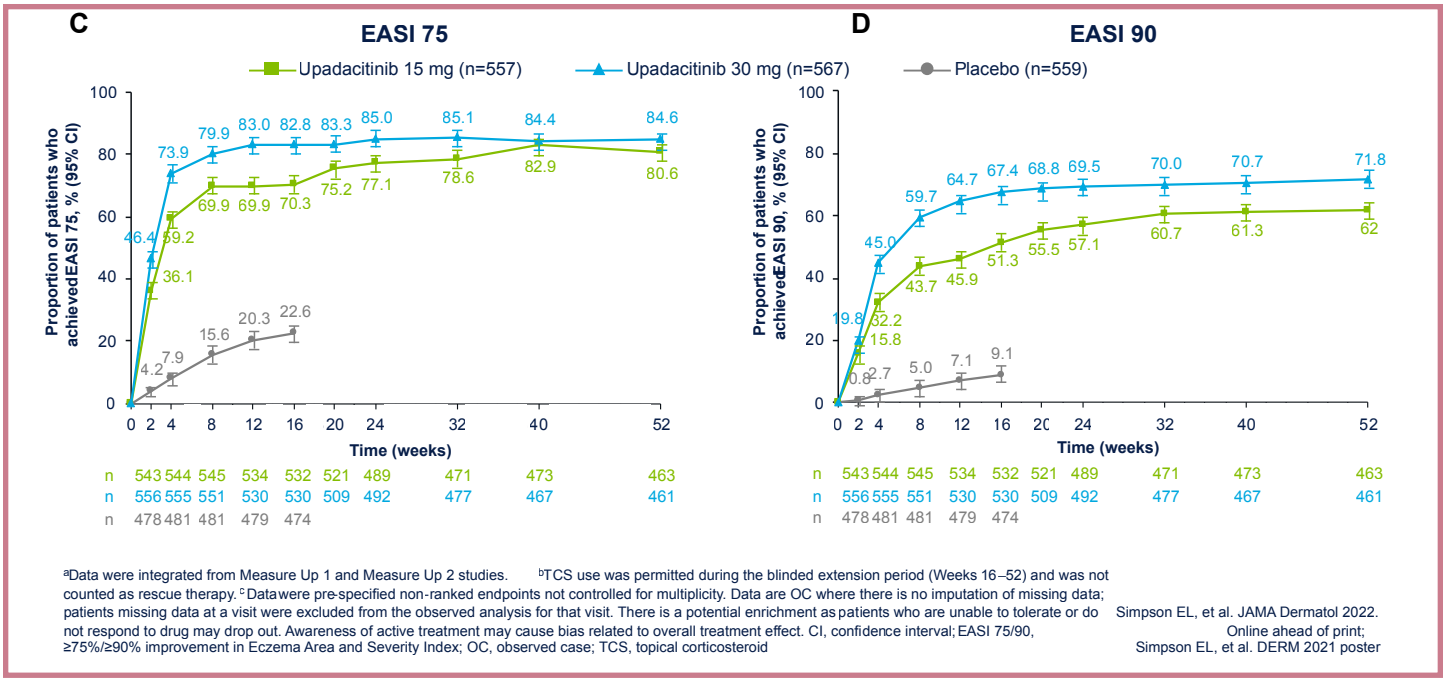
*p≤0.05; **p≤0.01; ***p≤0.001 vs placebo; p values are multiplicity controlled only at Week 16; p values are nominal at all other time points
[a]Based on ITT population, NRI-C CI, confidence interval; ITT, intent-to-treat for the main study; NRI-C, non-responder imputation incorporating multiple imputation to handle missing data due to coronavirus disease 2019; vIGA-AD 0/1, validated Investigator's Global Assessment for atopic dermatitis of clear (0) or almost clear (1) with ≥2 grades of reduction from baseline

The Heads Up study was a 24-week Phase 3b trial comparing oral upadacitinib 30 mg daily vs subcutaneous dupilumab, 300 mg every other week (n=692), as monotherapies. It demonstrated superiority of upadacitinib 30 mg daily over dupilumab injections at week 16 with EASI-75 response rates of 71% vs. 61.1% (p=0.006).[10] Significantly greater proportions of patients achieved high levels of efficacy on skin clearance (90% and 100% improvements in EASI score at baseline, EASI 90 and EASI 100, respectively) at week 16 with upadacitinib compared with dupilumab (EASI 90, 60.6% vs 38.7%; p<0.001; EASI 100, 27.9% vs 7.6%; p<0.001). All published upadacitinib clinical trials to date have met their primary and secondary endpoints (p<0.001 for all).[11] Importantly also, beyond improving skin lesions, upadacitinib demonstrated significant, rapid and sustained improvements in itch symptom measures as early one day after treatment initiation, which were maintained throughout 52-weeks of treatment.[8, 9]

Abrocitinib:

Abrocitinib (CIBINQO®) is also a systemic JAK1 selective inhibitor.[12] It was studied in the JADE trials for AD comparing abrocitinib 100 mg daily vs. abrocitinib 200 mg daily vs placebo, with or without TCS.* As an example, in JADE MONO 1, a total of 387 patients with moderate-to-severe AD were enrolled at 69 sites. Results demonstrated that when

*The Investigator's Global Assessment and EASI score utilized across the abrocitinib trials excluded scalps, palms and soles



[a]Data were integrated from Measure Up 1 and Measure Up 2 studies. [b]TCS use was permitted during the blinded extension period (Weeks 16–52) and was not counted as rescue therapy. [c]Data were pre-specified non-ranked endpoints not controlled for multiplicity. Data are OC where there is no imputation of missing data; patients missing data at a visit were excluded from the observed analysis for that visit. There is a potential enrichment as patients who are unable to tolerate or do not respond to drug may drop out. Awareness of active treatment may cause bias related to overall treatment effect. CI, confidence interval; EASI 75/90, ≥75%/≥90% improvement in Eczema Area and Severity Index; OC, observed case; TCS, topical corticosteroid

Simpson EL, et al. JAMA Dermatol 2022. Online ahead of print; Simpson EL, et al. DERM 2021 poster

Figure 1C and 1D. Integrated analysis of skin clearance at Week 52 by patients achieving EASI-75 and EASI-90; adapted from Simpson EL, et al. JAMA Dermatol 2022. Online ahead of print; Simpson EL, et al. DERM 2021 poster

abrocitinib was used as monotherapy, the EASI-75 response was significantly higher in the abrocitinib 200 mg and 100 mg group compared with placebo (63% vs. 40% vs 12% respectively, p<0·0001).[13] In the JADE-COMPARE study, a total of 838 subjects underwent randomization to receive 200 mg or 100 mg of abrocitinib orally once daily, or 300 mg of dupilumab subcutaneously every other week (after a loading dose of 600 mg), or placebo. An IGA response at week 12 was observed in 48.4% of patients in the 200 mg abrocitinib group, 36.6% in the 100 mg abrocitinib group, 36.5% in the dupilumab group, and 14.0% in the placebo group (P<0.001 for both abrocitinib doses vs. placebo). In addition, an EASI-75 response at week 12 was observed in 70.3% of patients on abrocitinib 200 mg, 58.7% of patients on abrocitinib 100 mg, 58.1% of patients on dupilumab, and 27.1% of patients on placebo (P<0.001 for both abrocitinib doses vs. placebo).[14]

Baricitinib:

Baricitinib (Olumiant®), is an oral JAK 1 and 2 inhibitor that is approved for the treatment moderate-to-severe rheumatoid arthritis in Canada. There have been several clinical trials using baricitinib in patients with AD. The BREEZE-AD5 study was a North American-based phase 3 monotherapy trial that enrolled 440 patients with moderate-to-severe AD. In this study, oral baricitinib at a dose of 2 mg daily appeared efficacious for moderate-to-severe AD vs placebo (EASI-75 at 16 weeks: 30% vs 8%, p < 0.001).[15] Baricitinib is not currently approved in Canada for the treatment of atopic dermatitis and will therefore not be discussed further in this supplement.

Comparative Efficacy of JAK Inhibitors:

Although there are no direct, head-to-head comparisons of the above JAK inhibitors, a recent review offers some insight. Silverberg et al. completed a network meta-analysis (NMA) to assesses the comparative efficacy of targeted systemic therapies in patients with moderate-to-severe AD based on randomized phase 2 and 3 studies. A NMA is a rather complex statistical methodology to compare multiple treatments and is ideal to gain perspective from pooling clinical trial data. A total of 11 trials encompassing 3339 patients treated with 5 different agents (abrocitinib, baricitinib, dupilumab, nemolizumab, and upadacitinib) were included in this analysis. The EASI-50 (or a 50% improvement from baseline in EASI score) response rate was highest for upadacitinib 30 mg QD, followed by abrocitinib 200 mg QD, upadacitinib 15 mg, and dupilumab 300 mg every 2 weeks. For itch improvements (ΔNRS ≥ 4), upadacitinib 30 mg also had the highest response rate, followed by abrocitinib 200 mg, upadacitinib 15 mg, and dupilumab. This rank order was also observed for EASI-75 and EASI-90 response rates. Limitations of this study include the absence of phase 3 data for all agents (upadacitinib only had phase 2b data), and variability in the primary endpoint timepoint across trials (12 weeks for abrocitinib and 16 weeks for other therapies).

Another group of authors also lead by Silverberg et al. completed a further NMA to assess the comparative efficacy of targeted systemic therapies in adults with moderate-to-severe AD based on the phase III monotherapy pivotal studies.[16] For this NMA, 11 unique phase 3 monotherapy trials encompassing 6254 patients treated with 5 different agents (abrocitinib, baricitinib, dupilumab, tralokinumab, or upadacitinib [or placebo]) were included. The EASI 75 response rate was highest for upadacitinib 30 mg, followed by abrocitinib 200 mg, upadacitinib 15 mg and dupilumab (**Figure 2**).

This rank order was also observed for the more stringent EASI-90 response rates, as well as for the itch improvements. Again, limitations included variable efficacy timepoints across the various trials (12 weeks for abrocitinib vs 16 weeks for other agents).

Of note, the above-mentioned NMA data related to clinical efficacy across phase 3 monotherapy trials may most accurately represent the real effect of the treatments as monotherapies (vs placebo), but is likely less representative of the current real-world utilization of targeted systemic therapies in moderate-to-severe AD, which are often utilized in combination with topical medications.[16] Clinicians should keep in mind the limited generalizability of NMA-based comparisons, which remain indirect and do not replace the value of head-to-head trials.

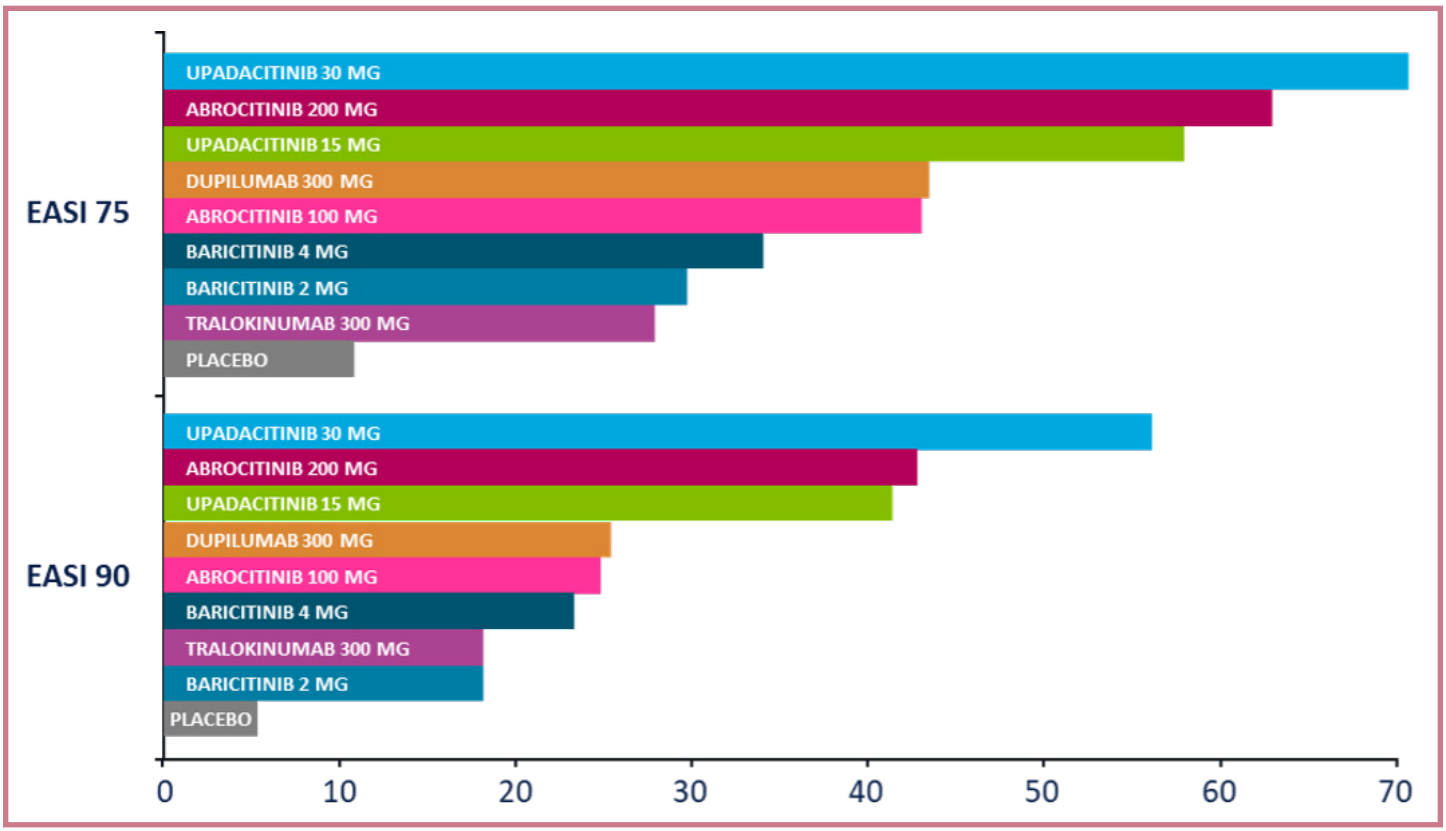


Figure 2. Systematic review and network meta-analysis of comparative efficacy of targeted therapies without topical corticosteroids; adapted from Silverberg JI, et al. Dermatol Ther (Heidelb) 2022. Online ahead of print.

EASI 75/90, ≥75%/90% improvement in Eczema Area and Severity Index

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Dr Wei Jing Loo is the owner and Medical Director of DermEffects, a cutting edge dermatology centre located in London, Ontario. Dr Loo completed medical school in 1997 with an honours degree from the University of New South Wales in Sydney, Australia. She trained in Internal Medicine and obtained membership in the Royal College of Physicians in the United Kingdom in 1999. She completed her dermatology residency training in Cambridge, United Kingdom and obtained her Certificate of Specialist Training in Dermatology in 2005. She is board certified in Canada and a fellow of the Royal College of Physicians and Surgeons of Canada. She is a member of the Canadian Dermatology Association and American Academy of Dermatology. Dr. Loo is at the forefront of the dynamic field of dermatology, serving as an associate investigator for Probity Medical Research. Dr. Loo is an Adjunct Professor at Western University in Ontario. She enjoys teaching and has presented at national and international meetings and published her work in many peer-reviewed journals.

JANUS KINASE INHIBITORS IN AD: A SAFETY OVERVIEW

The previous article in this special supplement provided an important overview of the pathophysiology and pivotal efficacy data of Janus kinase inhibitors (JAKis) in atopic dermatitis (AD). While efficacy is paramount to the clinician's decision-making approach to disease management, there is also a need to consider therapies that can be used in the long-term without causing irreversible end organ damage or high levels of adverse effects leading to treatment discontinuation.

First generation JAKis approved for the treatment of rheumatoid arthritis (RA) such as tofacitinib have exhibited a number of adverse events including severe infections, venous thromboembolism and malignancies, which have resulted in black box warnings[1]. Due to safety concerns with first generation JAK inhibitors, likely as a result of JAK2 and JAK3 inhibition, interest has shifted to the more selective JAK1 inhibitors with the aim of achieving a more tolerable safety profile [2,3]. Upadacitinib and abrocitinib have greater inhibitory potency for JAK1 than for JAK2, JAK3, or tyrosine kinase 2. Overall, the safety profile of the JAK1 inhibitors in the phase III AD studies, at the 16 week follow up timepoint, is reassuring (**Table 1**). These newer JAKis do not appear to have the same side effect profile as the first generation JAK inhibitors. As such, both compounds were recently approved for the treatment of adults and adolescents ≥ 12 years of age with refractory moderate-to-severe AD who are not adequately controlled with systemic treatments (e.g., steroid or biologic) or when use of those therapies is inadvisable.[4,5]

Importantly, upadacitinib and abrocitinib have been studied in a relatively younger and healthier AD population, which is very different from an older RA population who may have numerous underlying comorbidities, risk factors and possibly be taking concomitant immunosuppressive therapies. As a result, neither the indirect comparison across trials with differing patient populations nor the comparison of different JAKis with varying pharmacological characteristics and clinical profiles are recommended.

The Measure Up 1 and Measure Up 2 studies were 16-week replicate pivotal phase III studies designed to assess the safety and efficacy of upadacitinib vs placebo in moderate-to-severe AD patients. Eligible patients were adolescents

		Abrocitinib			Upadacitinib	
	PBO	**100 mg**	**200mg**	**PBO**	**15mg**	**30mg**
No. of patients (N)	211	370	364	902	899	906
	%	%	%	%	%	%
AI AEs	54-57	63-69	66-78	53-63	60-76	61-79
SAEs	1.3-4	3-5.4	1.3-3.6	2.5-3	1.8-2.4	0-3
Serious infection	1.3	1.9	0	0-1	0.4-24	0.7-1
VTE	0	0	0-1.8	0-0.4	0	0
Malignancy	0	0	0	0	0	0-1
Herpes simplex	1.8	0-1.8	0-2	1.7	3.3	7.7
Herpes zoster	0	0-1	0-1.3	0-1	0-2.2	1-2.1
Death	0	0-0.6	0	0	0	0
URTI	4-9	5-9	3-9	5-10	5-12	5-12
Nasopharyngitis	6-10	13-18	8-13	2.5-11	5-12	5-13
Nausea	2-3	2-9	14-20	2.5	2,4	7.1
Vomiting	0-1.3	0-1.3	0-5.2	NR	NR	NR
Headache	2.6-3.6	5.7-8.9	7.3-10	2.5-5.5	5-7	5-9.5
CPK elevation	0-2.6	0-1.9	0-3.2	2.3-5	4-7	5-9.5
Neutropenia	NR	NR	NR	0-1	1-4.8	1-5

Table 1. Summary of adverse events associated with systemic JAKis for the treatment of AD over short-term trials adapted from Wood et al., 2022[6]

AE, adverse event; SAE, serious adverse event; VTE, venous thromboembolism; URTI, upper respiratory tract infection; CPK, creatine phosphokinase; NR, not reported

(aged 12-17 years) and adults (aged 18-75 years) with moderate-to-severe atopic dermatitis (≥10% of body surface area affected by atopic dermatitis, Eczema Area and Severity Index [EASI] score of ≥16, validated Investigator's Global Assessment for Atopic Dermatitis [vIGA-AD] score of ≥3, and Worst Pruritus Numerical Rating Scale score of ≥4). The most frequently reported treatment-emergent adverse events (≥5% in any treatment group in either study) were acne (all but one were mild-moderate in severity, and usually managed via topical therapies or no intervention),[7] upper respiratory tract infection, nasopharyngitis and headache. The incidence of serious adverse events and adverse events leading to discontinuation of the study drug were low and balanced across treatment arms[8]. No deaths and few adverse events of special interest were reported in either study. The incidence of serious infections was less than 1% in all treatment groups; a few cases of opportunistic infections were reported, and the incidence was similar between treatment groups. All opportunistic infections reported were cases of eczema herpeticum (three patients in the upadacitinib 15 mg cohort, three patients in the upadacitinib 30 mg cohort, and four patients in the placebo cohort). The incidence of herpes zoster infection was higher in the active arms than the placebo arm. However, no cases of herpes zoster led to discontinuation of study drug. The incidence of anemia, neutropenia, and lymphopenia were observed to be transient. A few cases of malignancies excluding nonmelanoma skin cancer were noted, but none was deemed to be associated with the treatment. No cases of active tuberculosis, adjudicated gastrointestinal perforation, venous thromboembolic events, or major adverse cardiovascular events were reported in either of the upadacitinib cohorts. The Measure Up trials provided efficacy and safety data out to 16 weeks and more recently, 52-week efficacy and safety data demonstrated an overall consistency with the 16-week data for both doses of upadacitinib (**Table 2**).[9]

Recent studies have also published safety data on other JAKis showing adverse event rates over an average duration of 24 or more weeks.[10-12] In an integrated analysis of a phase IIb study, four phase III studies, and one long-term extension study to evaluate the long-term safety of abrocitinib 200 mg and 100 mg, total exposure in the all-abrocitinib cohort (n = 2856) was 1614 patient-years (PY); exposure

		Week 16		Week 52	
Events/100 PY	**PBO (n=559) PY=156.0**	**UPA 15 mg (n=557) PY=167.9**	**UPA 30 mg (n=567) PY=169.9**	**UPA 15 mg (n=797) PY=953.3**	**UPA 30 mg (n=811) PY=978.2**
Any TEAE	455.2	518.1	637.0	252.0	301.7
Serious AEs	11.5	7.7	10.0	6.8	8.5
AEs leading to discontinuation of study drug	15.4	10.1	13.0	4.5	7.2
Deaths	0	0	0	0	0.1b
Most frequently reported TEAEs (≥10 events/100 PY in any treatment group at any time point)					
Acne	7.7	33.4	55.3	13.1	20.3
URTI	23.7	28.0	38.3	12.2	11.4
Nasopharyngitis	25.6	24.4	34.1	9.9	10.9
Headache	16.7	22.6	24.7	7.4	6.7
Blood CPK increased	8.3	16.7	17.7	7.0	11.1
Oral herpes	3.2	7.1	14.7	3.3	7.1
Diarrhea	9.0	10.7	11.2	3.4	3.5
Folliculitis	5.1	6.0	11.2	3.5	4.0
Neutropenia	1.3	2.4	10.6	1.0	2.9
Cough	5.8	9.5	10.0	4.7	2.9
Dermatitis atopic	35.9	10.1	4.7	8.9	5.3
Nausea	2.6	10.7	9.4	2.3	2.8
Serious infections	1.9	1.8	2.4	2.2	3.6
Eczema herpeticumc	2.6	3.0	2.4	1.9	1.9
Herpes zoster (HZ)	1.3	6.6	5.3	3.6	5.4
NMSC	0	1.8	0.6	0.4	0.4
Malignancy other than NMSC	0	0	1.8	0.2	0.5
Lymphoma	0	0	0.6	0	0.1
Adjudicated MACE	0	0	0	0.1	0
Adjudicated venous thromboembolic event	0.6	0	0	0.1	0.1

Table 2. Treatment-emergent adverse events and exposure-adjusted event rates during upadacitinib administrationa; adapted from Guttman-Yasky, E. et al, 2021

[a]Combined data from Measure Up 1 and Measure Up 2 studies (safety population). [b]One death (myocardial infarction related to COVID-19 infection) occurred on study Day 399 (28 days after last study drug dose) in a 67-year-old man treated with UPA 30 mg in Measure Up 1; the patient had multiple cardiovascular disease risk factors. AE, adverse event; CPK, creatine phosphokinase; PBO, placebo; PY, patient-year; TEAE, treatment-emergent AE; UPA, upadacitinib; URTI, upper respiratory tract infection; [c]Eczema herpeticum or Kaposi's varicelliform eruption

CPK, creatine phosphokinase; GI, gastrointestinal; HZ, herpes zoster; MACE, major adverse cardiovascular event; NMSC, non-melanoma skin cancer; PBO, placebo; PY, patient-year; TB, tuberculosis; UPA, upadacitinib

was ≥ 24 weeks in 1248 patients and ≥ 48 weeks in 606 patients (maximum 108 weeks)[10]. Results from this study demonstrated that dose-related AEs (200 mg, 100 mg, placebo) were nausea (14.6%, 6.1%, 2.0%), headache (7.8%, 5.9%, 3.5%), and acne (4.7%, 1.6%, 0%). A transient and dose-dependent reduction in platelet count was observed; 2/2718 patients (200 mg group) had confirmed platelet counts of < 50 × 10^3/mm^3 at week 4. Incidence rates (IRs) were 2.33/100PY and 2.65/100PY for serious infection, 4.34/100PY and 2.04/100PY for herpes zoster, and 11.83/100PY and 8.73/100PY for herpes simplex in the 200 mg and 100 mg groups, respectively. The IRs for nonmelanoma skin cancer, other malignancies, and major adverse cardiovascular events were observed to be < 0.5/100PY for both doses. Five venous thromboembolism events occurred (IR 0.30/100PY), all in the 200 mg group.

To date, the long-term safety data for newer JAK inhibitors up to 52 weeks of treatment is consistent across the published literature of the JAK inhibitor class with no new safety signals being reported. The upadacitinib 52-week data looking at the exposure-adjusted adverse event rates (per 100 patient-years) remained stable between 16 and 52 weeks of exposure (**Table 2**). Longer term data up to 5 years will be available in the near future, and which, when combined with real world experience, may enhance physician comfort with prescribing new generation JAKis for their AD patients.

Screening and monitoring considerations with JAKis in AD

Before initiating therapy with JAKis, it is important to ensure that key vaccinations are up to date including prophylactic zoster vaccination in agreement with current immunization guidelines [9]. Clinicians should also assess for signs and symptoms of infection, screen for TB or latent TB by performing a TB skin test or QuantiFERON®-TB Gold and order a chest x-ray. It is important to verify the pregnancy status of female patients of childbearing age. Clinicians should also screen for risks factors for VTEs including birth control use, prothrombotic status, past history or family history of deep vein thrombosis/pulmonary embolism. Finally, baseline bloodwork should include CBC, aspartate transaminase/alanine transaminase (AST/ALT), renal function, lipid profile and hepatitis serology.

Despite an acceptable safety profile, monitoring is required with JAKis. It is recommended to see patients for follow up a few months after initiating JAKi therapy to check clinical response, side effects and to repeat basic bloodwork which would include CBC, liver enzymes and lipid profile (**Table 3**).

		Evaluate no later than			
X Upadacitinib X Abrocitinib	Evaluate at baseline	4 weeks after treatment initiation	12 weeks after treatment initiation	Thereafter evaluate according to routine patient management or clinical guidelines	Treatment should not be initiated or continued
Laboratory parameters					
Lymphocytes (ALC)	XX	X	X	XX	In patients with: <0.5 x 10^9 cells/L
Neutrophils (ANC)	XX	X	X	XX	In patients with: <1 x 10^9 cells/L
Platelets	X	X		X	<50 x 10^9 cells/L
Hemoglobin (Hb)	XX	X	X	XX	<80 g/L
Lipids	X X	X	X (at 12 weeks)	XX	
Liver enzymes (AST/ALT)	X			X	AST/ALT increase indicative of suspected liver injury

Table 3. Key monitoring considerations with JAKis for the treatment of AD

Conclusion

JAK inhibitors have revolutionized the treatment landscape for moderate-to-severe atopic dermatitis. As novel small molecules with a unique mode of action involving the blocking of the JAK-STAT pathway, JAKis are highly, rapidly efficacious and have demonstrated a tolerable safety profile in the AD population. The side effects associated with JAKi use are largely minor, highly predictable and can be readily identified through regular monitoring and easily managed with no long term sequelae observed out to >1 year in adults and adolescents with moderate-to-severe atopic dermatitis.

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