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SPECIAL SUPPLEMENT

THE EVIDENCE AND CLINICAL RATIONALE FOR THE USE OF JAK INHIBITORS IN THE MANAGEMENT OF AD

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THE EVIDENCE AND CLINICAL RATIONALE FOR THE USE OF JAK INHIBITORS IN THE MANAGEMENT OF AD

Introduction:

Atopic dermatitis (AD) is one of the most common chronic inflammatory skin diseases affecting 1 in 5 children and 1 in 10 - 20 adults.[1-3] AD is characterized by clinical symptoms and signs of erythema, edema, excoriation, lichenification, xerosis, and in pediatric populations, oozing and weeping is more prevalent.[4] Intense itch associated with AD can negatively impact sleep and quality of life. The consequences of sleep disturbance and fatigue may be underdiagnosed in this population.[5]

Atopic dermatitis has been associated with medical comorbidities that fall within type 2 inflammatory conditions (e.g., such as asthma, allergic rhinoconjunctivitis, and food allergies) as well as non-type-2 inflammatory conditions such as cardiometabolic disease, infections (both cutaneous and non-cutaneous), anxiety/depression, and autoimmune conditions such impetigo and alopecia aerata.[6-8] AD has the strongest impairment of life expectancy outside of malignancy when it comes to dermatologic disease.[9]

While topical therapies such as topical corticosteroids (TCS), topical calcineurin inhibitors (TCI), and phosphodiesterase 4 (PDE4) inhibitors are effective treatments for most patients with mild-to- moderate AD, more than 90% of those suffering from moderate-to-severe AD report significant unmet need along with the use of multiple therapeutic options, including off-label systemic medications which do not offer symptom control.[10] Patients with refractory disease commonly receive acute courses oral corticosteroids, if not chronic treatment with systemic therapies, either off-label immunosuppressive agents (e.g., methotrexate) or the immunomodulator dupilumab (a monoclonal antibody) targeting components of the inflammatory signature characterizing moderate-to-severe AD.

In this paper we review and summarize the role and clinical application of an emerging class of systemic targeted therapy, namely the oral Janus kinase inhibitors (JAKi) in the treatment and management of moderate-to-severe AD.

Pathophysiology and Immunology:

AD is multifactorial and driven by a complex interplay of epidermal barrier dysfunction and immune dysregulation that results in chronic inflammation. The pathophysiology of the disease involves both host genetics, epigenetics, and environmental interactions.[11-13]

A dysfunctional barrier from the proteins of epidermal differentiation (e.g. filaggrin) and the tight junctions (the primary barrier against transepidermal water loss: e.g., claudins) are coupled with decreased very long chain fatty acids and ceramides. This results in increased permeability to microbial antigens including allergens, chemical and physical irritants, and toxins from entering and meeting the immune system, particularly with reduced antimicrobial peptides present from immune dysregulation[13] impairs the normal defense response to environmental pathogens.[14-16]

In most patients, although non type-2 inflammation is present in AD, there is a higher prevalence towards type 2 inflammation. Cytokines associated with type 2 inflammation such as IL-4, IL-5, IL-13, and IL-31 are found in increased quantities in affected patients.[17,18] These mechanisms are described in **Figure 1**. Interestingly, apart from type-2 cytokines, a number of non-type-2 inflammatory mediators are increasingly recognized as potential contributors to the heterogenous pathophysiology observed in patients living with moderate-to-severe AD, depending on phases of the disease (acute vs chronic) as well as patient ethnicity/ hereditary factors.[19-21] Non-type-2 cytokines suspected of playing roles in the pathogenesis of AD include Th17, Th1, Th22 cytokines, but also cytokines of the IL-1 family and alarmins.

The rationale for JAK inhibitors:

Many of the key cytokine receptors involved in immune dysregulation that skews toward Type 2 and Type 22 (T helper 2 [Th2] and 22 [Th22]) inflammation in acute stages of AD, as well as activation of Th1, Type 2 and Th17 pathways in chronic phases and/or some genetic backgrounds are activated via JAK and STAT proteins.

Pro-inflammatory cytokines including type 2 cytokines, "thymic stromal lymphopoietin (TSLP)" and IFN-γ transduce signals via the JAK1 pathway and are involved in atopic dermatitis pathogenesis (**Figure 2**).[21]

JAK-STAT proteins bind to the intracellular portion of type I/II cytokine receptors that are responsible for recognizing soluble inflammatory mediators of cytokines. Typically the JAK proteins become activated and phosphorylate STAT proteins which dimerize and translocate to the nucleus (**Figure 2**). The gene transcription is affected in a transcriptional domain that leads to further cytokine, chemokine production as well as other immune processes.

For example, JAK-STAT pathways play a critical role in the dysregulation of immune responses in AD, including the exaggeration of Th2 cell response, the activation of eosinophils, the maturation of B cells, and the suppression of regulatory T cells. As such IL-4-mediated JAK-STAT activation upregulates epidermal chemokines, pro-inflammatory cytokines, and pro-angiogenic factors, while downregulating antimicrobial peptides and factors responsible for skin barrier function in AD.[24]

Since 2017, the dupilumab monoclonal antibody targeting the IL-4R alpha chain administered by subcutaneous injection every 2 weeks has been available in Canada for the treatment of moderate-to-severe AD when disease is not adequately controlled with topical treatment.[25] The Phase 3 duplicate studies LIBERTY AD SOLO 1 and 2 enrolled adults with moderate-to-severe AD whose disease was inadequately controlled by topical treatment. Patients were randomly assigned in a 1:1:1 ratio to receive, for 16 weeks, subcutaneous dupilumab (300 mg) as a monotherapy, or placebo weekly or the same dose of dupilumab every other week alternating with placebo. The primary outcome was the proportion of patients who had both a score of 0 or 1 (clear or almost clear) on the Investigator's Global Assessment (IGA) and a reduction of 2 points or more in that score from baseline at week 16.[26]

In SOLO 1, the primary outcome-- a score of 0 or 1 (clear or almost clear) on the IGA and a reduction of 2 points or more in that score from baseline at week 16-- occurred in 85 patients (38%) who received dupilumab every other week and in 83 (37%) who received dupilumab weekly, as compared with 23 (10%) who received placebo ($p<0.001$ for both comparisons with placebo). The results were similar in SOLO 2, with the primary outcome occurring in 84 patients (36%) who received dupilumab every other week and in 87 (36%) who received dupilumab weekly, as compared with 20 (8%) who received placebo ($p<0.001$ for both comparisons). In addition, in the two trials, an improvement from baseline to week 16 of at least 75% on the Eczema Area and Severity Index (EASI 75) was reported in significantly more patients who received each regimen of dupilumab than in patients who received placebo ($P<0.001$ for all comparisons). With respect to adverse events, injection-site reactions and conjunctivitis were more frequent in the dupilumab groups than in the placebo groups.[26]

Given the pathophysiology and immunology of AD, inhibition of intracellular JAK-STAT pathways may address the immune dysregulation present in AD. Given the heterogeneity of inflammatory signatures as well as dysregulated Th2, Th1 and Th17 pathways in some populations and individuals, it would be potentially advantageous to target a broader array of immune activation.

The early published evidence establishing the use of JAKi for the treatment of AD, provides clinicians with head-to-head comparison studies for 2 of the JAKi agents, upadacitinib and abrocitinib, vs. dupilumab. These studies will be reviewed in the next section. Upadacitinib was approved in Canada in 2019 for the treatment of adults with moderate-to-severe active rheumatoid arthritis, the treatment of adults with active psoriatic arthritis and for the treatment of adults and adolescents 12 years of age and older with refractory moderate-to-severe AD who are not adequately controlled with a systemic treatment (e.g., steroid or biologic) or when use of those therapies is inadvisable.[22] Upadacitinib has demonstrated greater inhibitory potency at JAK1 relative to JAK2, JAK3 and TYK2 and is currently available in 15 mg and 30 mg extended-release tablet format, the latter dose being only approved for AD.[22] Abrocitinib is currently under review by Health Canada.

HEADS UP STUDY:

The HEADS UP study was a randomized double-blinded, double dummy Phase 3b trial comparing the safety and efficacy of upadacitinib 30 mg* once-daily versus 300 mg subcutaneous dupilumab every other week in adults with moderate-to-severe AD. In this study, 692 patients were randomized 1:1 to receive either upadacitinib 30 mg orally once daily or dupilumab 300 mg subcutaneously every 2 weeks, with follow up for 24 weeks.[27] The baseline severity of AD was measured using validated instruments such as EASI (16 or more), Validated Investigator Global Assessment scale for Atopic Dermatitis (vIGA-AD of 3 or more), Worst Pruritus Numerical Rating Scale (WP-NRS of 4 points of more), and a minimum of 10% body surface area (BSA) affected. Patients needed to be candidates for systemic therapy, but prior use of JAK inhibitors or dupilumab was prohibited. Efficacy was assessed as upadacitinib superiority compared with dupilumab, with the primary end point being EASI 75 at week 16. Secondary end points were: percentage change from baseline in WP-NRS, achievement of EASI 100 and EASI 90 at week 16, percentage change from baseline in WP-NRS at week 4, achievement of EASI 75 at week 2, percentage change from baseline in WP-NRS at week 1, and WP-NRS improvement of 4 points or more at week 16.[27]

** The recommended starting dose of upadacitinib is 15 mg for adults, while the 30 mg is recommended for those not adequately responding to 15 mg or those initially presenting with severe disease.*

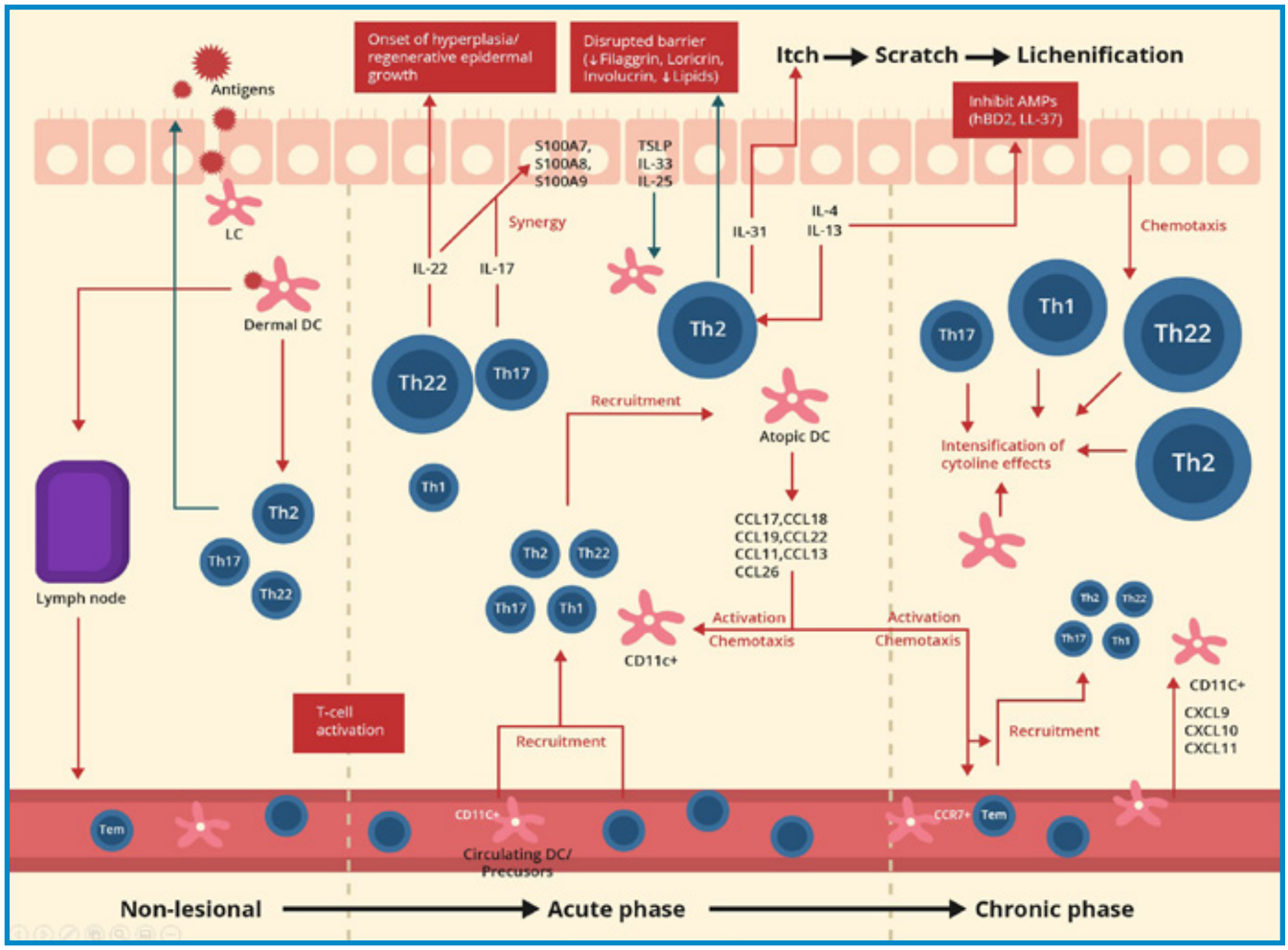

Figure 1. *The immunology of atopic dermatitis from skin to blood; image courtesy of Evidence Based Medical Educator Inc.*

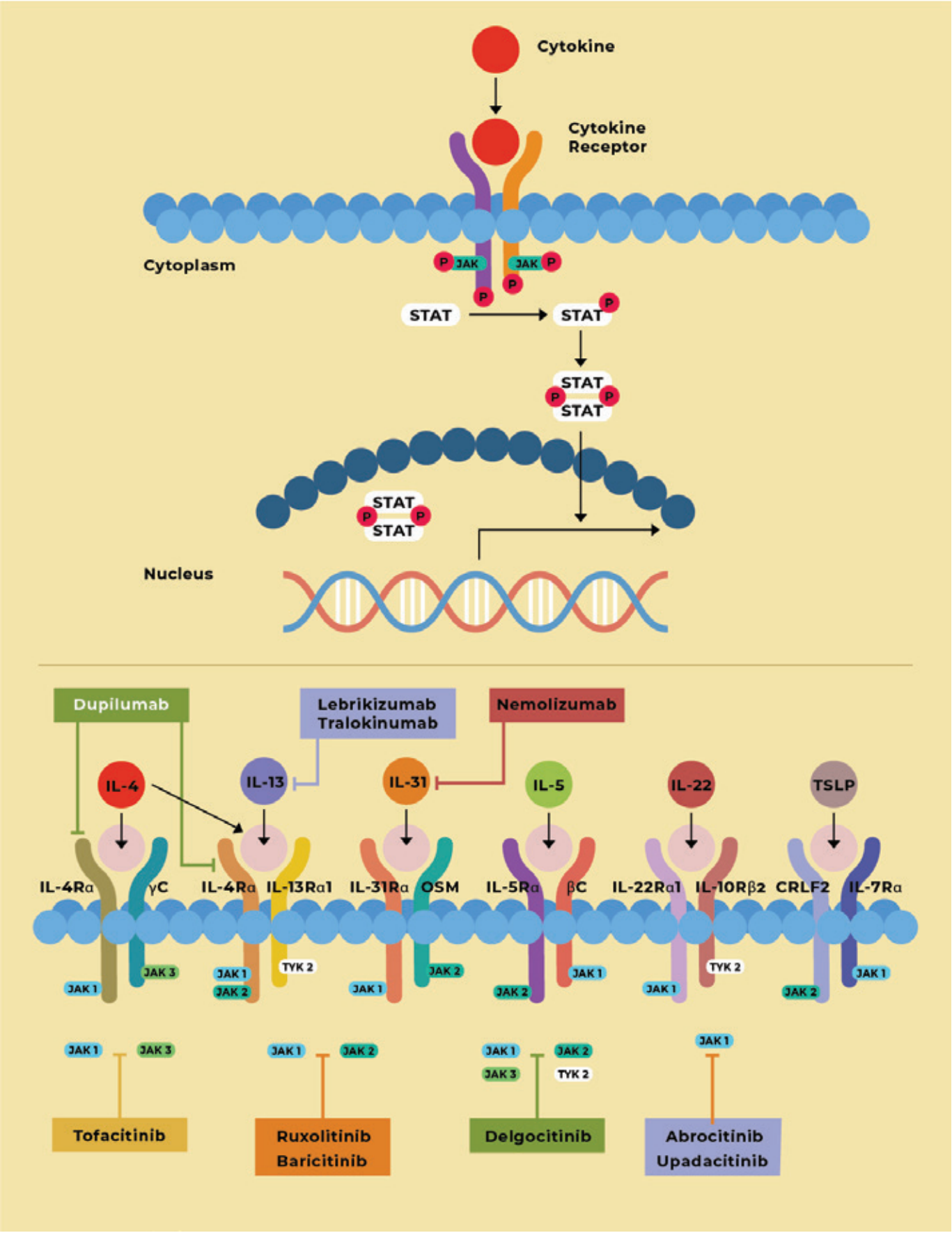

Figure 2. *Upper portion showing how a cytokine affects a receptor to induce intracellular cascade of phosphorylation events in STATs that go down into the nuclear. Lower portion denotes different cytokine receptors, their cytokines, and intracellular activation through JAKs of other pathways as well as potential therapeutic targets shown in coloured boxes; image courtesy of Evidence Based Medical Educator Inc.*

The proportion of patients who achieved the primary endpoint of EASI 75 at week 16 was significantly greater for patients receiving upadacitinib than those receiving dupilumab (247 [71.0%] vs 210 [61.1%]; adjusted difference, 10.0% (95% CI, 2.9%-17.0%; p=0.006). All secondary endpoints were also met including improvement in WP-NRS as early as week 1 favoring upadacitinib-treated patients compared with dupilumab-treated patients (31.4% [1.7%] vs 8.8% [1.8%]; p<0.001) and proportion of patients achieving EASI 75 at week 2 in 43.7% of patients on upadacitinib versus 17.4% of patients on dupilumab (152 of 348 [43.7%] vs 60 of 344 [17.4%]; p<0.001).[27] (**Figure 3A-3D**)

When looking at treatment emergent adverse events, the rate of serious AEs and serious infections remained low in both arms, however, they were slightly higher with upadacitinib (**Table 1**). The most common AE reported by ≥5% of subjects in either treatment group included acne with upadacitinib (15.8%) and conjunctivitis with dupilumab (8.4%).

In either group, there were no reports of active tuberculosis (TB), lymphoma, major adverse cardiovascular events (MACE) or venous thromboembolic event (VTE).

In the interim analysis of the open-label extension (OLE) HEADS UP study period, 245 patients initially on dupilumab and 239 patients initially on upadacitinib were treated with open label upadacitinib 30 mg once daily for an additional 16 weeks. Of those patients who did not achieve EASI 75/90 with dupilumab in the initial Heads Up study, 87.5/78% achieved EASI 75/90 after 16 weeks of open-label upadacitinib treatment (**Figure 4**). Additionally, 57.7% of patients who did not achieve WP-NRS improvement at week 24 with dupilumab, achieved it at 16 weeks with upadacitinib. Patients initially treated with upadacitinib maintained their response with further upadacitinib treatment. There were no new safety signals observed with upadacitinib.[28]

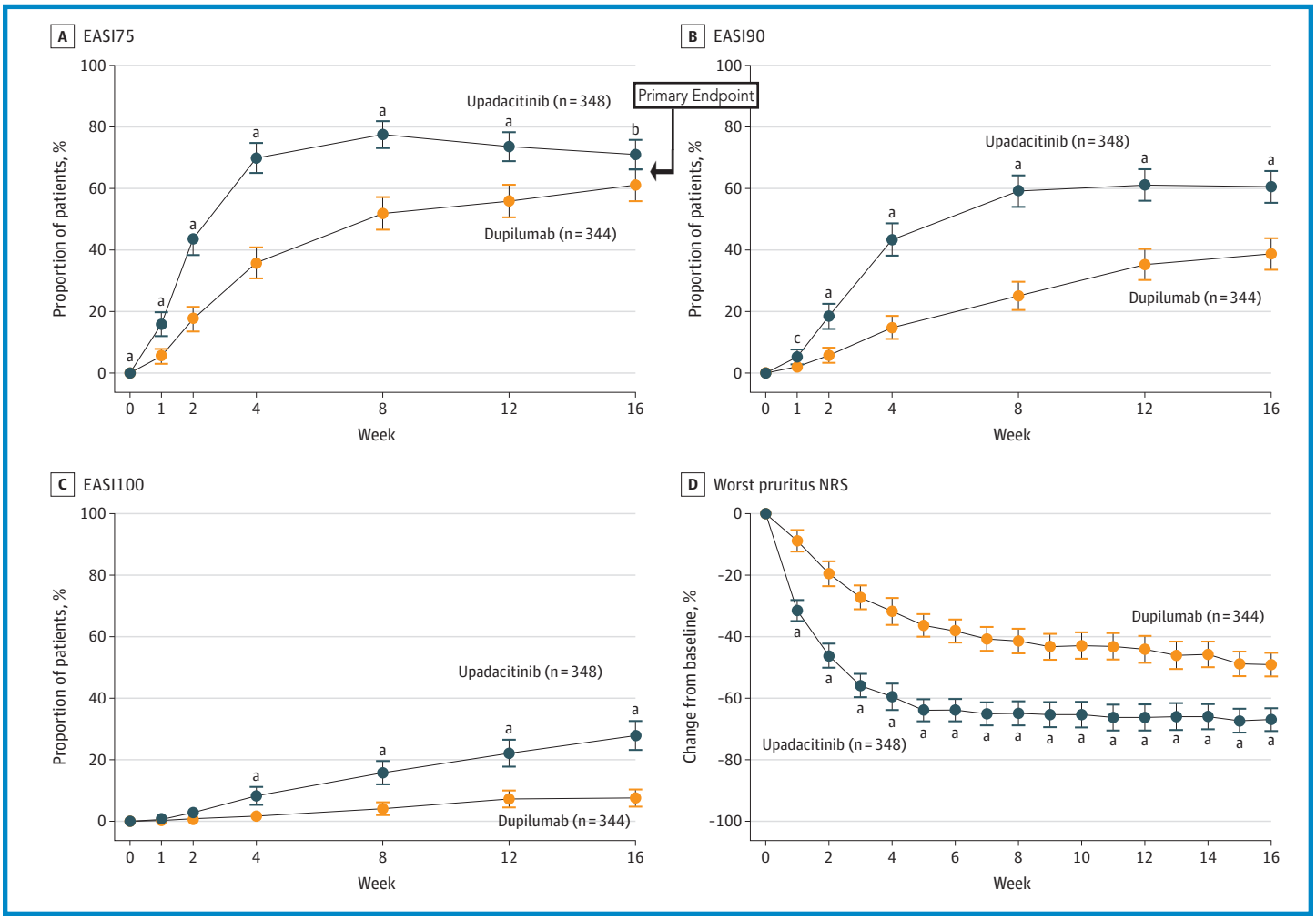

Figure 3A-3D: *Efficacy Over Time A, Proportion of patients achieving 75% improvement in Eczema Area and Severity Index (EASI75) B, Proportion of patients achieving 90% improvement in EASI (EASI90). C Proportion of patients achieving 100% improvement in EASI (EASI100). D, Mean percentage change in Worst Pruritus Numerical Rating Scale (NRS) for patients treated with upadacitinib or dupilumab by nonresponder imputation incorporating multiple imputation to handle missing data due to COVID-19. Error bars indicate 95% CIs (synthetic result based on t test distribution from the PROC MIANALYZE procedure in SAS if there were missing data due to COVID-19 or was based on the normal approximation to the binomial distribution if there were no missing data due to COVID-19).*

[a]P ≤ .001.; [b]P ≤ .01.; [c]P ≤ .05.

JADE COMPARE STUDY:

The JADE COMPARE study was a phase 3, double blinded, double dummy, placebo controlled trial evaluating the efficacy and safety of two abrocitinib doses (200 mg or 100 mg orally once daily), 300 mg dupilumab subcutaneously every 2 weeks (after a loading dose of 600 mg), or placebo in 838 adults with moderate-to-severe AD already on background topical therapy. The primary end points were an IGA response (defined as a score of 0 [clear] or 1 [almost clear] on the IGA [scores range from 0 to 4], with an improvement of ≥2 points from baseline) and an EASI 75 response at week 12 for both abrocitinib doses vs placebo. Secondary end points included IGA/EASI 75 at week 16 and itch response using Peak Pruritus Numerical Rating Scale (PP-NRS) at week 2 as the only pre-specified endpoint comparing abrocitinib with dupilumab.[29]

A total of 838 patients were randomized at a 2:2:2:1 ratio. The abrocitinib 200 mg group showed the greatest efficacy with an IGA response at week 12 in 48.4% of patients. The abrocitinib 100 mg group (36.6%) and the dupilumab group (36.5%) achieved similar week 12 responses, while the placebo arm demonstrated a 14.0% response rate ($p<0.001$ for both abrocitinib doses vs placebo). The EASI 75 at week 12 demonstrated similar findings with a 70.3% response at week 12 for the higher dose abrocitinib group, and again similar results for lower dose abrocitinib and dupilumab groups at 58.7% and 58.1% respectively ($p<0.001$ for both abrocitinib doses vs. placebo). The placebo group was at 27.1%. The 200-mg dose, but not the 100-mg dose, of abrocitinib was superior to dupilumab with respect to itch response at week 2.[29]
Results at week 16 revealed no significant difference between either of the two doses of abrocitinib and dupilumab with respect to EASI 75 or IGA (these comparisons were not pre-specified).[29] In terms of safety, more total adverse events were observed in the abrocitinib 200 mg group than the other groups, but serious adverse events remained low in all groups. Nausea and acne seemed to be more prominent in the abrocitinib groups while conjunctivitis was more frequent in the dupilumab group. There were a total of 6 cases of uncomplicated herpes zoster in the abrocitinib groups.[29]

The JADE EXTEND study was undertaken to assess the proportion of dupilumab non responder patients from JADE COMPARE who experienced clinically meaningful improvement in signs and symptoms of AD after switching to abrocitinib. Investigators concluded that a substantial proportion of dupilumab nonresponders achieved clinically meaningful improvement in signs (IGA, EASI-75, EASI-90) and symptoms (PP-NRS4, PP-NRS 0/1) of moderate-to-severe AD after switching to abrocitinib.[30]

JADE DARE STUDY:

The JADE DARE study was a 26-week, double blinded, double dummy, phase 3 study comparing abrocitinib 200 mg administered once daily by oral tablet and dupilumab 300 mg administered subcutaneously every other week after a 600 mg loading dose. Similarly to the JADE COMPARE study, JADE DARE study arms also used a background topical therapy. The co-primary efficacy endpoints in JADE DARE were the proportion of patients achieving at least a 4-point improvement in the severity of PP-NRS from baseline at Week 2 and the proportion of patients achieving EASI 90 (≥90% improvement from baseline) at Week 4. The key secondary endpoint was the proportion of patients achieving EASI 90 at Week 16. The study will allow assessment of any difference in efficacy that may persist at month 6 of treatment. Both primary endpoints and key secondary endpoints were met, and the safety profile seen with abrocitinib was consistent with previous studies in the JADE program.[31]

DISCUSSION:

It is clear that there is a mechanistic basis for the use of JAKi in the treatment of AD with clinical trials demonstrating excellent efficacy and safety with different JAKi currently available. Head-to-head studies using upadacitinib and abrocitinib (both at their high dose of 30 mg and 200 mg once-daily, respectively) show a faster onset of action and superior reduction of signs/symptoms of AD compared with dupilumab. The superiority of high-dose upadacitinib over dupilumab was more notable across more stringent endpoints, like EASI 90 and even EASI 100. The emergence of therapies achieving higher efficacy threshold represents an important step towards improving the standard of care for moderate-severe AD patients. Similarly, open-label extension studies point to patient improvement in key endpoints when switching from dupilumab to upadacitinib with no loss of efficacy nor increased adverse events in patients with severe AD.

The newer JAKi offer several potential advantages over other therapies for the treatment of AD including oral administration, and a clean safety profile including a lack of conjunctivitis as seen with dupilumab. However, there are differences related to this class of drug's immunosuppressive profile and include the need for safety monitoring and the recommendation to bring patients up to date with all immunizations in conjunction with current immunization guidelines prior to initiating treatment. JAKi inhibitors are also associated with serious warnings and precautions related to an increased risk of serious infections, malignancies and thrombosis as shown in the literature with differentially selective JAKi for different indications. Careful assessment of patient antecedents, risk factors as well as monitoring for such events is recommended before/after treatment initiation. Finally, JAKi should not be used in pregnant individuals or those who may be trying to get pregnant or who are lactating.

Despite the advantages of these newer JAKi, dupilumab has a larger body of real-world evidence and experience and requires no monitoring. While most patients may prefer oral tablets over frequent injections, some patients may perceive bi-weekly dosing as an advantage over oral daily dosing. Those patients having comorbid conditions with other type 2 inflammatory conditions such as severe asthma and chronic sinusitis with nasal polyps may also benefit from treatment with dupilumab.[32-34]

Conversely, patients suffering from rheumatologic or autoimmune conditions including rheumatoid arthritis or psoriatic arthritis may benefit from JAK inhibition.[35,36]

Evidence from head-to-head studies suggest that a high-dose JAKi, such as upadacitinib monotherapy, may be superior to dupilumab monotherapy on clinical dimensions related to skin clearance and itch reduction, especially across higher efficacy thresholds. JAKi may even offer

TEAE	Patients, No. (%)	
	Dupilumab, 300 mg (n = 344)	Upadacitinib, 30 mg (n = 348)
AE	216 (62.8)	249 (71.6)
AE with reasonable possibillty of being drug-related[a]	122 (35.5)	153 (44.0)
Severe AE	14 (4.1)	25 (7.2)
SAE	4(1.2)	10(2.9)
SAE with reasonable possibility of being drug-related[a]	2(0.6)	4(1.1)
A leading to discontinuation of Study drug	4(1.2)	7(2.0)
A leading to death[b]	0	1(0.3)
AEs of special interest		
Serious Infections	2(0.6)	4(1.1)
Opportunistic Infection, excluding tuberculosis and herpes zoster[c]	0	1(0.3)
Herpes zoster	3(0.9)	7(2.0)
Active tuberculosis	0	0
Nonmelanoma skin cancer[d]	1(0.3)	0
Mallignant neoplasm, excluding NMSC	0	0
Lymphoma	0	0
Hepatic disorder[e]	4(1.2)	10(2.9)
Adjudicated gastrointestinal perforations	0	0
Anemia	1(0.3)	7(2.0)
Neutropenia	2(0.6)	6(1.7)
Lymphopenia	0	2(0.6)
Creatine phosphokinase elevation	10(2.9)	23(6.6)
Renal dysfunction	1(0.3)	1(0.3)
Adjudicated major adverse cardiovascular events	0	0
Adjudicated venous thromboembolic events	0	0
TEAEs reported by ≥ 5% in either treatment group		
Acne[f]	9(2.6)	55(15.8)
Dermatitis atopic	29(8.4)	24(6.9)
Upper respiratory tract infection	13(3.8)	22(6.3)
Blood CPK level increased	10(2.9)	23(6.6)
Nasopharyngitis	22(6.4)	20(5.7)
Headache	21(6.1)	14(4.0)
Conjunctivitis	29 (8.4)	5(1.4)

Table 1. *TEAEs Through Week 16 for All Patients Receiving 1 Dose or More of Study Drug; adapted from Blauvelt et al 2021*

Abbreviations: AE, adverse event; CPK, creatine phosphokinase; NMSC, nonmelanoma skin cancer; SAE, serious AE; TB, tuberculosis; TEAE, treatment-emergent adverse event. [a] *As assessed by investigator.* [b] *A 40-year-old woman who had bronchopneumonia associated with influenza A was found deceased at home on study day 70.* [c] *All opportunistic infections were eczema herpeticum.* [d] *Keratoacanthoma, no reasonable possibility of association with study drug according to the investigator.* [e] *Hepatic disorders: most were elevated transaminase levels.* [f] *Most acne events consisted primarily of inflammatory papules, pustules, and comedones, involving the face. All events were nonserious. None led to treatment discontinuation.*

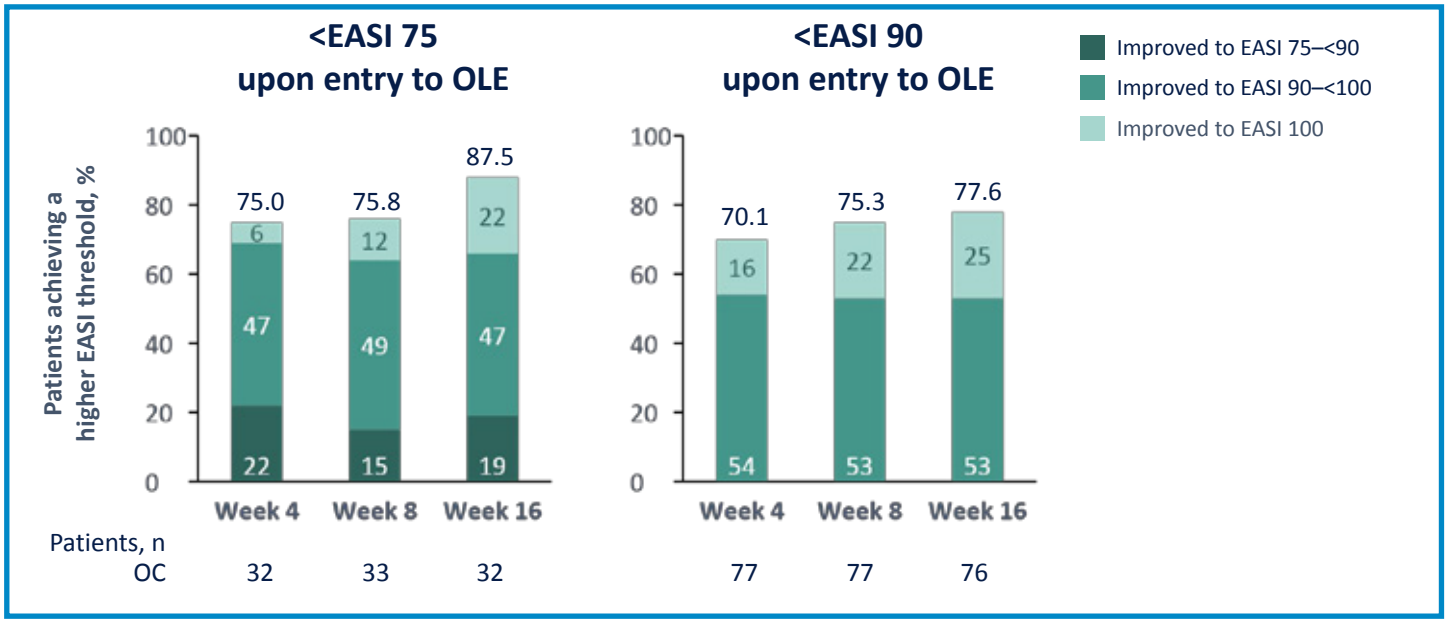

Figure 4. Improvement in Clinical Response After Switching from Dupilumab to Upadacitinib (ITT Population, OC); Blauvelt et al, Presentation for the 30th European Academy of Dermatology and Venereology Congress, 28 September–2 October 2021, EADV Virtual Congress

EASI, Eczema Area and Severity Index; DUPI, dupilumab; UPA, upadacitinib, OC, observed case analysis, ITT, intent-to-treat population

compelling advantages in patients who do not respond adequately to dupilumab. High-dose JAK1 inhibition with upadacitinib and abrocitinib both demonstrated a favorable risk-benefit profile as well as a faster onset of clinical response compared with dupilumab.

As always, shared decision making between patients and clinicians including a balanced review of risks, benefits, and alternatives of each therapy is recommended in choosing the optimal therapy. By complementing advances in the treatment armamentarium of moderate-to-severe AD that followed the approval of dupilumab, the emergence of JAK inhibitors provides patients and clinicians with additional options to achieve specific treatment goals and to advance care for this heavily burdened patient population.

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