ABOUT THE AUTHOR

Wei Jing Loo, BSc, MBBS, MRCP, FRCP

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 published her work in many peer-reviewed journals.

Affiliations:
Adjunct Professor, University of Western Ontario, London, ON

ADVANCED THERAPIES FOR MODERATE-TO-SEVERE ATOPIC DERMATITIS: MARATHON OR SPRINT?

Introduction

Atopic dermatitis (AD) is a chronic, relapsing and remitting disease that has a substantial impact on the lives of patients and caregivers.[1] While mild AD can be adequately managed with topical therapies, patients with moderate-to-severe AD may require systemic treatment[2] which has traditionally consisted of off-label use of immunosuppressants such as methotrexate, cyclosporine, and azathioprine.[3]

Several advanced therapies that target specific components of the pathophysiological pathway in AD are now available for patients with moderate-to-severe disease.[4] Agents approved in Canada include an anti–interleukin (IL)-4 receptor inhibitor that blocks signalling of both IL-4 and IL-13 (dupilumab), a selective anti–IL-13 monoclonal antibody (tralokinumab), and selective Janus kinase (JAK) inhibitors (abrocitinib and upadacitinib) (**Table 1**).[5-8] The introduction of these therapies has greatly improved dermatologists' ability to tailor treatment strategies based on individual clinical profiles and patient preferences.

Although a short time to onset of symptomatic improvement is important to AD patients and their physicians, durability, and sustainability of therapy are critical for optimizing long-term outcomes and patient satisfaction with treatment. Clinical trials of tralokinumab have provided unique long-term maintenance data that have practical relevance to clinicians, including dose de-intensification and response recapture after dose interruptions.[9-12] The goal of this article is to review evidence for the efficacy and safety of long-term maintenance therapy with tralokinumab in adults with moderate-to-severe AD.

Interleukin-13 in Atopic Dermatitis

AD has traditionally been considered a predominantly IL-4–dependent disease, given the role of this cytokine in IgE synthesis and the characterization of AD as an allergic inflammatory skin condition driven by the type 2 immune response.[13] Although both IL-4 and IL-13 play a role in the pathogenesis of AD, a recent large-scale transcriptomic study showed overexpression of IL-13, but not IL-4, in skin biopsy samples from patients with AD.[14] Additionally, a meta-analysis of genome-wide association studies

demonstrated that the gene for IL-13 was one of three (along with those for filaggrin and OVOL1) most strongly associated with the risk of developing AD.[15] Furthermore, expression of IL-13 in skin lesions found in patients with AD has been strongly associated with disease severity,[13,16,17] and IL-13 can stimulate itch-sensory neurons to cause pruritus.[18,19] Therefore, specifically targeting IL-13 has become an important therapeutic strategy in AD.[13]

Tralokinumab in Atopic Dermatitis

Pivotal clinical trials

The clinical efficacy and safety of tralokinumab for adults with moderate-to-severe AD were assessed in the Phase III randomized ECZTRA 1, ECZTRA 2, and ECZTRA 3 trials.[9-11] ECZTRA 1 and ECZTRA 2 were identically designed studies in which patients were randomized to receive tralokinumab or placebo every 2 weeks (q2w) for 16 weeks, followed by a 36-week maintenance period in which tralokinumab-treated patients who achieved a pre-specified clinical response at Week 16 were re-randomized to tralokinumab q2w, tralokinumab every 4 weeks (q4w), or placebo.[9] In ECZTRA 3, patients were randomized to receive tralokinumab q2w plus topical corticosteroids (TCS) PRN or placebo q2w plus TCS for 16 weeks, followed by a 16-week maintenance period in which tralokinumab responders at Week 16 were re-randomized to tralokinumab q2w or q4w.[10]

In all three trials, tralokinumab was associated with significant improvements vs placebo on the co-primary endpoints of achieving an Investigator's Global Assessment (IGA) score of 0 or 1 (IGA 0/1) and ≥75% improvement in Eczema Area and Severity Index (EASI 75) at Week 16.[9,10] In addition, a significantly greater proportion of patients in the tralokinumab group than in the placebo group achieved clinically meaningful improvements from baseline on numerous patient-reported outcomes (PROs) within one to three weeks of treatment initiation. This included the Worst Daily Pruritus Numerical Rating Scale (NRS), eczema-related sleep disturbance (SD) NRS, Dermatology Life Quality Index (DLQI), and Patient-Oriented Eczema Measure (POEM) scores.[20] Tralokinumab treatment for 16 weeks was also associated with increased microbial diversity and reduced *Staphylococcus aureus* abundance (which contributes to epidermal barrier defects) in the AD lesional skin vs placebo, as assessed using lesional skin samples from patients in ECZTRA 1.[21] In ECZTRA 3, although patients in both groups were permitted to use TCS as needed, concomitant TCS use was significantly lower in tralokinumab-treated patients than in patients receiving placebo at Week 16.[11]

The early positive outcomes reported at Week 16 were maintained through Week 52 in ECZTRA 1 and 2[9] and Week 32 in ECZTRA 3,[10] with progressive improvements in efficacy over time.[11] Notably, a *post hoc* analysis of 32-week data from ECZTRA 3 identified a subgroup of patients who achieved high response rates in the Eczema Area Severity Index [(EASI) 75 or EASI 90)] following just 4 weeks of treatment.[11]

Rates of adverse events (AEs) and serious AEs (SAEs) in ECZTRA 1, 2, and 3 were similar between the initial and maintenance treatment periods, and between groups within each period, with few treatment discontinuations due to AEs.[9,10] Conjunctivitis was an AE of special interest (AESI) and was reported more frequently with tralokinumab than with placebo; however, most cases were mild-to-moderate in severity, resolved by the end of the treatment period, and very rarely led to treatment discontinuation.

Collectively, data from the ECZTRA trials provides strong evidence for the efficacy and safety of tralokinumab treatment for up to one year. However, as AD is a chronic disease, longer-term data are critical to support clinical decision-making.

ECZTEND

The ECZTEND trial is an ongoing, five-year, open-label extension trial investigating the long-term safety and efficacy of tralokinumab in patients who completed a tralokinumab parent trial.[12] All participants in ECZTEND receive tralokinumab 300 mg q2w plus optional TCS, regardless of prior treatment in the parent trials. The primary endpoint is the number of AEs during the treatment period from baseline to Week 268; secondary endpoints are the proportions of patients achieving IGA 0/1 and EASI 75. A *post hoc* interim analysis of ECZTEND reported safety data for all adult participants at the April 30, 2020 data cut-off (safety analysis set), and an analysis of a two-year cohort of patients on tralokinumab for 52 weeks in ECZTRA 1/2 and for 56 weeks in ECZTEND (**Figure 1**).[12,22] Patients in the two-year cohort were subdivided into three groups to account for varying intervals between parent trials and first dose in ECZTEND: ≤5 weeks (continuous treatment), 6-15 weeks (interrupted) and >15 weeks (washout).[12]

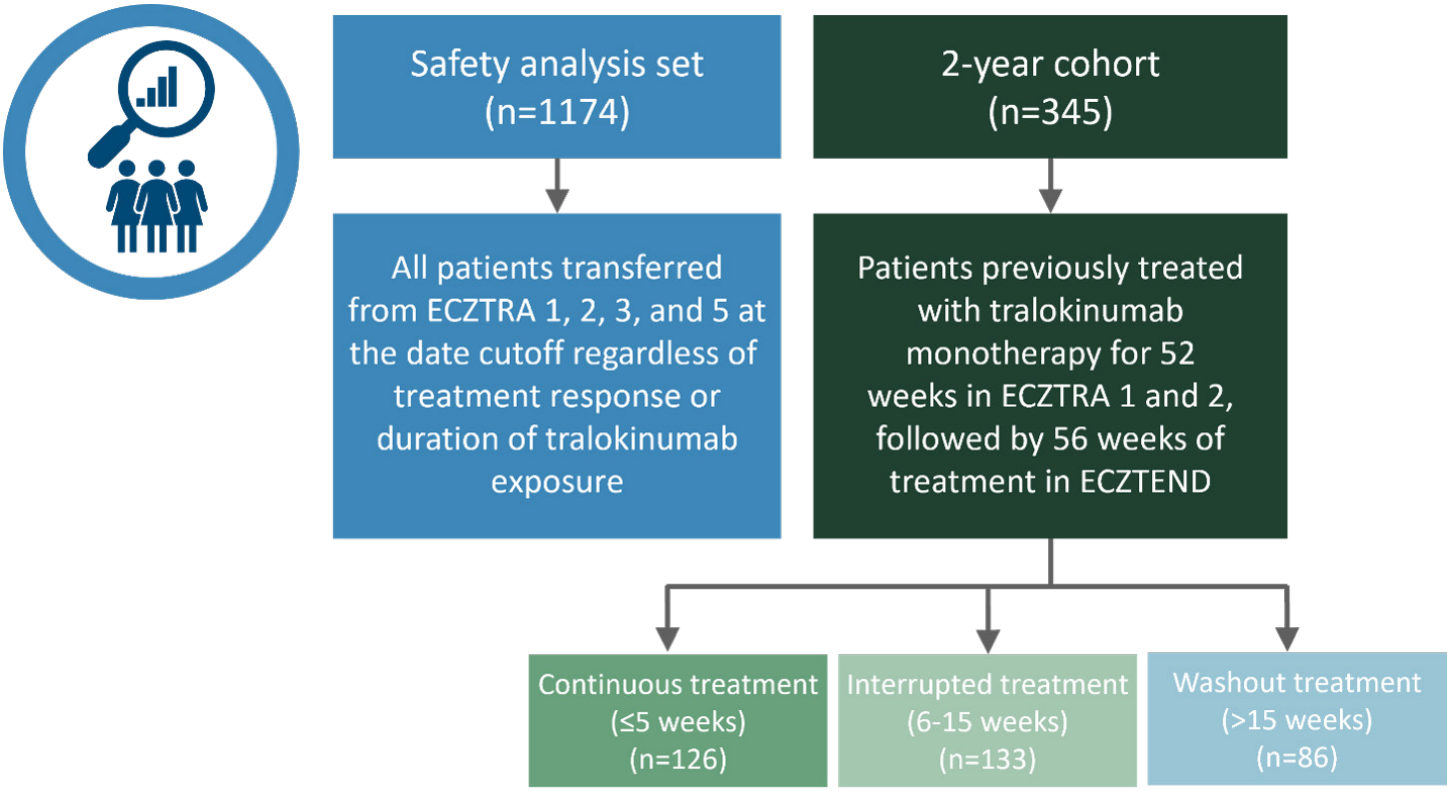

Figure 1. *Patient cohorts in ECZTEND interim analysis (April 2020 data cut). Adapted from Blauvelt et al, 2022.*[12]

Long-term use of tralokinumab was well tolerated and the safety profile was consistent with that of the parent trials (**Table 2**).[12,22] Approximately 95% of AEs were mild or moderate in severity, and no deaths were reported in the interim safety analysis.[12] In both the safety analysis set and two-year cohort, there was a low incidence of conjunctivitis reported with tralokinumab (n=45 [3.8%] and n=17 [4.9%], respectively).[12,22] Rates of conjunctivitis reported with dupilumab were relatively higher in a 3-year open-label extension trial (n=521/2677 [19.5%]).[23] Most cases of conjunctivitis with tralokinumab were mild or moderate and resolved with or without ophthalmologic treatment when tralokinumab was discontinued.[12] Only two patients reported severe conjunctivitis and one patient discontinued tralokinumab due to a conjunctivitis-related AE. No drug-associated facial or neck erythema events were observed with tralokinumab, which is notable given previous reports of these AEs in clinical practice with dupilumab.[24] Nonetheless, real-world data for tralokinumab will be necessary to determine whether such events arise in clinical practice.

In the two-year cohort, patients showed progressive and sustained improvements in signs and symptoms of AD, with 69.6%, 50.4% and 40.6% of patients achieving EASI 75, EASI 90, and IGA 0/1, respectively (**Table 3**).[12] Tralokinumab resulted in similar efficacy across the continuous, interrupted and washout groups. In the parent trials, the median percentage improvement in EASI following one year of tralokinumab was 88.0%, and this further increased to 91.7-92.7% by the end of ECZTEND (**Figure 2**). Notably, the efficacy achieved with tralokinumab appeared to be sustained even following >15 weeks of treatment interruption, as the washout group was still able to achieve a 68.6% improvement in EASI from the parent trial baseline to the ECZTEND baseline. Furthermore, participants in the interrupted and washout subgroups regained improvements similar to those achieved at the end of the parent trials by Week 12 of treatment in ECZTEND. Practically, this suggests that patients who flare on tralokinumab q4w dosing would be expected to recapture their earlier response by reducing the dosing interval to q2w, or by re-starting tralokinumab if treatment were interrupted for extended periods of time.

	Tralokinumab [ADTRALZA®][6]	Dupilumab [DUPIXENT®][5]	Abrocitinib [CIBINQO®][7]	Upadacitinib [RINVOQ®][8]
Mechanism of Action	• IL-13 inhibitor	• IL-4/IL-13 receptor inhibitor	• JAK1 inhibitor	• JAK1 inhibitor
Approved indication(s) in Canada[a]	• AD: Adults and adolescents aged ≥12 years	• AD: Patients aged ≥6 years • Also approved for asthma and CRSwNP	• AD: Patients aged ≥12 years	• AD: Adults and adolescents aged ≥12 years • Also approved for RA, PsA, and AS
Dosing[b]	• Initial dose of 600 mg followed by 300 mg q2w • At prescriber's discretion, q4w dosing may be considered for some patients who achieve clear or almost clear skin following 16 weeks of treatment	• Initial dose of 600 mg followed by 300 mg q2w	• 100 mg or 200 mg PO once daily	• 15 mg or 30 mg PO once daily
Use in special populations	• Preferable to avoid during pregnancy • Considerations for benefit of breastfeeding to child versus benefit of therapy to woman when breastfeeding	• Dose adjustments based on body weight recommended for pediatric patients aged 6-17 years • Considerations for benefit of breastfeeding to child versus mother's clinical need for therapy and potential risks to child	• Dose adjustments recommended in: » Elderly patients » Pediatric patients » Patients with moderate or severe renal impairment » Patients on strong CYP2C19 and moderate CYP2C9 inhibitors • Not recommended with concomitant use of CYP2C19/2C9 inducers • Should not be used during breastfeeding • Should not be used during pregnancy unless clearly necessary	• Dose adjustments recommended in: » Elderly patients » Pediatric patients » Patients with severe renal impairment » Patients on strong CYP3A4 inhibitors • Not recommended in patients with severe hepatic impairment • Should not be used during breastfeeding • Should not be used during pregnancy • Not recommended with concomitant use of strong CYP3A4 inducers
Monitoring requirements	• N/A	• N/A	• Hematology • Lipids • Liver enzymes • Signs of infection and viral reactivation • Musculoskeletal enzymes in symptomatic patients • Periodic skin examination for patients at increased risk of skin cancer	• Hematology • Lipids • Liver enzymes • Musculoskeletal enzymes in symptomatic patients • Signs of infection and viral reactivation • Signs and/or symptoms of cancer
Boxed warnings	N/A	N/A	• Serious infections including TB • Malignancies • Venous thromboembolism • MACE	• Serious infections including TB • Malignancies • Venous thromboembolism • MACE

Table 1. *Comparison of advanced therapies approved for the treatment of moderate-to-severe AD in Canada; courtesy of Wei Jing Loo, MD*
a For a complete list of approved indications, consult Health Canada Product Monographs.
b Additional or more detailed adjusted or alternate dosing schedules may be described in the Product Monographs but are not included herein.
AD, atopic dermatitis; AS, ankylosing spondylitis; CRSwNP, chronic rhinosinusitis with nasal polyposis; IL, interleukin; JAK, Janus kinase; MACE, major adverse cardiovascular events; N/A, not applicable; PO, oral; PsA, psoriatic arthritis; q2w, every two weeks; q4w, every four weeks RA, rheumatoid arthritis; TB, tuberculosis.

	ECZTEND safety analysis set[a] Tralokinumab q2w + optional TCS (n = 1,174; PYE = 1,235.7)		ECZTEND overall two-year cohort[b] Tralokinumab (n = 345; PYE = 420.8)	
	n (%)	Rate (nE/100 PYE)	n (%)	Rate (nE/100 PYE)
Summary				
All AEs	844 (71.9)	237.8	280 (81.2)	246
Severity				
Mild	695 (59.2)	158.2	223 (64.6)	158
Moderate	435 (37.1)	72.1	152 (44.1)	78.4
Severe	62 (5.3)	7.5	24 (7.0)	9.5
Serious AEs	55 (4.7)	4.8	17 (4.9)	4
AEs leading to study withdrawal	19 (1.6)	1.5	7 (2.0)	1.7
Most frequently reported AEs (≥5% of participants)				
Viral URTI[c]	250 (21.3)	29.3	95 (27.5)	32.3
Dermatitis atopic	158 (13.5)	20.6	50 (14.5)	16.6
URTI	83 (7.1)	9.1	34 (9.9)	11.6
Conjunctivitis	45 (3.8)	4.5	17 (4.9)	5.5
Headache	49 (4.2)	5.7	17 (4.9)	5.7

Table 2. *Summary of adverse events with tralokinumab in the ECZTEND safety analysis population and overall two-year cohort. Adapted from Blauvelt et al, 2022[12] and Blauvelt et al, 2021[22]*
a Trial initiation to April 30, 2020.
b Patients from ECZTRA 1 / 2 enrolled in ECZTEND ≥60 weeks prior to data cut-off (April 30, 2020) – safety analysis set.
c Most commonly reported as the common cold.
AE, adverse event; nE, number of events; PYE, patient-years of exposure; q2w, every two weeks; URTI, upper respiratory tract infection.

Study	Tralokinumab 300 mg q2w	Tralokinumab 300 mg q4w	Placebo	P value
ECZTRA 1[a]	60.0%	49.0%	33.0%	0.056
ECZTRA 2[a]	56.0%	51.0%	21.0%	<0.001
ECZTRA 3[b]	92.5%	90.8%	NR	NR
ECZTEND[c]	69.6%	N/A	N/A	NR

Table 3. *Summary of long-term EASI 75 outcomes with tralokinumab in the ECZTRA parent trials (ECZTRA 1/2 and ECZTRA 3) and ECZTEND interim analysis. Adapted from Abduelmula et al, 2023[25] and Blauvelt et al, 2022.[12]*
a Proportion of patients maintaining EASI 75 response at Week 52 who achieved EASI 75 at Week 16 with tralokinumab monotherapy.
b Proportion of patients maintaining EASI 75 response at Week 32 who achieved EASI 75 at Week 16 with tralokinumab/placebo + concomitant topical corticosteroids.
c Proportion of patients with EASI 75 response at 2 years (two-year overall cohort, restricted to subjects who received treatment with tralokinumab for 52 weeks in the ECZTRA 1/2 parent trials, followed by treatment with tralokinumab for 56 weeks in ECZTEND).

All data reported using non-responder imputation (NRI).
NR, not reported; N/A, not applicable.

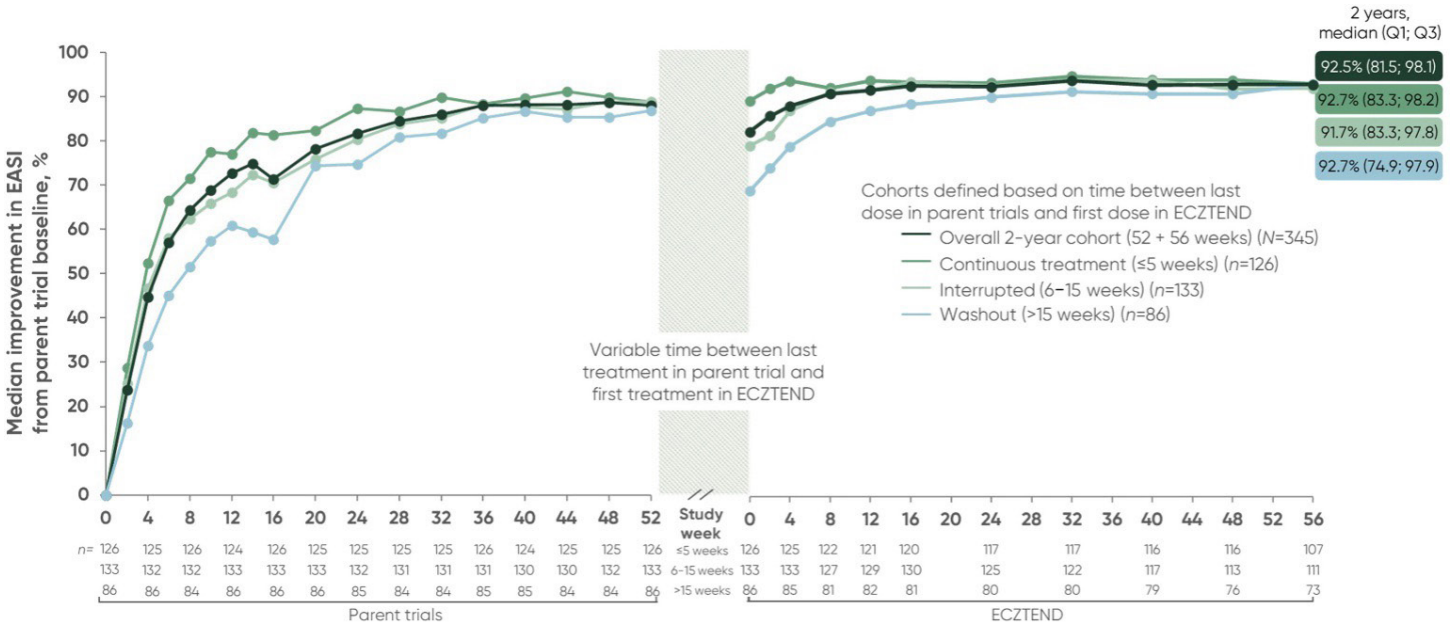

Figure 2. *Median percentage improvement in EASI from parent trial baseline through 2 years of tralokinumab treatment (Week 56 in ECZTEND). Adapted from Blauvelt et al, 2022.*[12]
Note: variable intervals between Week 52 of the parent trials and the first dose in ECZTEND are denoted as continuous (interval ≤5 weeks), interrupted (interval 6-15 weeks), or washout (interval >15 weeks) groups. Parent trial data shown herein include only participants who entered ECZTEND.

EASI, Eczema Area and Severity Index.

Conclusion

For patients who live with chronic, relapsing and remitting conditions such as AD, clinical management more closely resembles a marathon than a sprint. Although quick relief of signs and symptoms is important from both the patient and physician perspectives, durability and sustainability of efficacy, as well as safety, are critical. Importantly, evidence from the ECZTRA trials indicates that patients who achieve clear or almost clear skin with initial q2w dosing may be extended to q4w dosing at the clinician's discretion, with clinical response being maintained in many cases.[9–11] Data from ECZTEND supports that a response can be recaptured by resuming tralokinumab treatment among patients who lose some efficacy even after a washout period of more than 15 weeks.[12] These unique attributes of tralokinumab may help support treatment decision-making for patients and clinicians.

Correspondence:
Dr. Wei Jing Loo
Email: dermeffects@gmail.com

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