Indirect Treatment Comparison of First-Line Biologic Treatments in Adolescents with Moderate to Severe Atopic Dermatitis: A Systematic Literature Review and Network Meta Analysis

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INTRODUCTION

- Adolescents with moderate-to-severe atopic dermatitis (AD) have a high disease burden
- Treatment options for adolescents with moderate-to-severe AD remain limited[1]
- Clinical guidelines strongly recommend both dupilumab and tralokinumab over continued standard topical treatment without those agents for adolescents[2,3]
- There is a lack of head-to-head trials directly comparing biologic therapies in this setting
- **OBJECTIVE:** To compare efficacy and safety measures in clinical trials of first-line biologic interventions in adolescents with moderate-to-severe atopic dermatitis

METHODS

SYSTEMATIC LITERATURE REVIEW

- Conducted in accordance with PRISMA-NMA guidance
- Inclusion criteria shown in **Table 1**

NETWORK META ANALYSIS (NMA)

- NMA was conducted in the Bayesian framework using noninformative priors
- Markov Chain Monte Carlo simulation; 3 chains; 20,000 iterations; Gibbs sampling algorithm
- Both fixed effects and random effects models were compared for best model fit

Table 1: Inclusion Criteria

Category	Inclusion Criteria
Population	• Adolescent patients aged 12-17 years with moderate-to-severe atopic dermatitis that is inadequately controlled by topical treatments
Intervention	• Biologic systemic treatments
Comparator	• Placebo
Outcomes	**Primary** • IGA 0/1 score at week 16 • EASI-75 score at week 16 **Secondary** • Peak Pruritus NRS score improvement ≥4 points at week 16 • CDLQI at week 16 • Adverse events
Study Design	• Randomized controlled trials
Setting	• Any
Geography	• Any
Language	• English language articles and abstracts
Publication Date	• 1 Jan 2013 to 30 Sep 2023

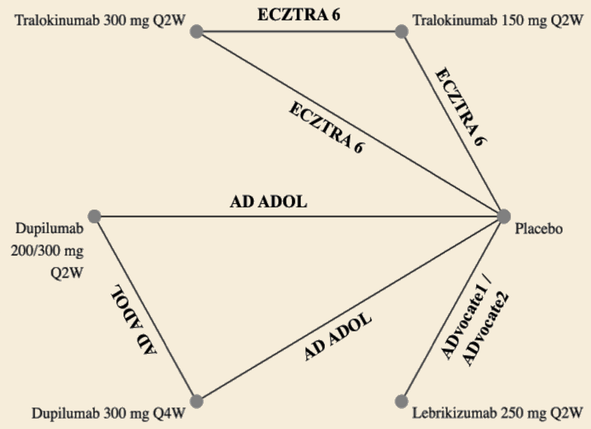
CDLQI = Children's Dermatology Life Quality Index (0-30 scale: higher the score, greater the handicap); EASI-75 = 75% Improvement from Baseline in Eczema Area and Severity Index Score (0-72 scale: 0 = clear; 50.1-72 = very severe AD); IGA = Investigator's Global Assessment (0-4 scale: 3 = moderate; 4 = severe); NRS = Numerical Rating Scale (0-10 scale: 0 = no itch; 10 = worst itch imaginable)

- Categorical variables (EASI-75 and IGA 0 and 1) evaluated using risk ratios
- Continuous outcome (CDQLI) evaluated using standardized mean difference
- Heterogeneity statistic (I^2) calculated to quantify variability in results across studies
- League table illustrates effect sizes evaluated using surface under the cumulative ranking (SUCRA) values of the likelihood of each treatment rank relative to one another
- Certainty of evidence evaluated using Confidence in Network Meta-Analysis (CINeMA) tool
- Analysis conducted in R using GemTC

RESULTS

- 13 reports included, with 3 assessed treatments (**Figure 1**)
- Baseline population demographic and clinical characteristics are similar except for prior systemic treatments (**Table 2**)
- Network graph used to visualize direct relationships between active treatment and placebo (**Figure 2**)
- With fixed effects model, all treatments were more efficacious than placebo in achieving primary outcomes of EASI-75 and IGA 0/1 at 16 weeks (**Table 3**)
- The SUCRA indicate that dupilumab 200/300 mg Q2W had highest probability of ranking first in achieving an EASI-75 (31%), IGA 0/1 (67%), peak pruritus NRS score improvement ≥4 points (41%) at week 16

Figure 2: Network Graph



Q2W = every 2 weeks; Q4W = every 4 weeks

Table 3: Outcome League Table for EASI-75, IGA Score 0/1, Peak Pruritus NRS Score Improvement ≥4 Points, CDQLI at Week 16

EASI-75 RR (95% CrI)	DUP 200/300mg Q2W					
	1.1 (0.7, 1.6)	DUP 300mg Q4W				
	1.3 (0.4, 4.1)	1.2 (0.4, 3.7)	LEB 250mg Q2W			
	1.2 (0.3, 3.7)	1.1 (0.3, 3.4)	0.9 (0.3, 3.0)	TRA 300mg Q2W		
	1.1 (0.3, 3.6)	1.0 (0.3, 3.3)	0.9 (0.3, 2.9)	1.0 (0.6, 1.5)	TRA 150mg Q2W	
	5.2 (2.6, 12.0)	**4.7 (2.3, 12.0)**	**3.8 (2.0, 9.8)**	**4.6 (2.1, 13.0)**	**4.5 (2.0, 12.0)**	**PBO**
IGA 0/1 RR (95% CrI)	DUP 200/300mg Q2W					
	1.4 (0.8, 2.5)	DUP 300mg Q4W				
	3.4 (0.7, 26.0)	2.5 (0.5, 18.0)	LEB 250mg Q2W			
	2.7 (0.4, 22.0)	1.9 (0.3, 16.0)	0.8 (0.2, 16.0)	TRA 300mg Q2W		
	2.2 (0.3, 17.0)	1.6 (0.2, 13.0)	0.6 (0.1, 2.5)	0.8 (0.5, 1.5)	TRA 150mg Q2W	
	12.0 (3.3, 78.0)	**8.6 (2.3, 56.0)**	**3.4 (1.6, 10.0)**	**4.6 (1.7, 17.0)**	**5.6 (2.2, 20.0)**	**PBO**
Peak Pruritus NRS Score Improvement ≥4 Points RR (95% CrI)	DUP 200/300mg Q2W					
	1.4 (0.9, 2.2)	DUP 300mg Q4W				
	2.1 (0.5, 9.4)	1.5 (0.4, 6.7)	LEB 250mg Q2W			
	1.0 (0.2, 5.1)	0.7 (0.1, 3.6)	0.5 (0.1, 2.2)	TRA 300mg Q2W		
	1.1 (0.2, 5.5)	0.8 (0.1, 4.1)	0.5 (0.1, 2.6)	1.1 (0.7, 1.8)	TRA 150mg Q2W	
	8.3 (3.4, 28.0)	**6.0 (2.4, 20.0)**	**4.0 (1.7, 13.0)**	**7.6 (2.6, 35.0)**	**8.3 (2.8, 37.0)**	**PBO**
CDQLI SMD (95% CrI)	DUP 200/300mg Q2W					
	0.6 (0.3, 0.8)	DUP 300mg Q4W				
	-2.2 (-2.7, -1.8)	-2.8 (-3.2, -2.4)	TRA 300mg Q2W			
	-3.2 (-3.6, -2.7)	-3.7 (-4.2, -3.3)	-0.9 (-1.2, -0.7)	TRA 150mg Q2W		
	-6.3 (-6.6, -6.0)	-6.9 (-7.2, -6.6)	-4.1 (-4.4, -3.8)	-3.1 (-3.4, -2.9)	PBO	

CDQLI = Children's Dermatology Life Quality Index; DUP = dupilumab; EASI-75 = 75% Improvement from Baseline in Eczema Area and Severity Index Score; IGA = Investigator's Global Assessment; LEB = lebrikizumab; NRS = Numerical Rating Scale; RR = risk ratio; SMD = standardized mean difference; TRA = tralokinumab

Figure 1: PRISMA Diagram

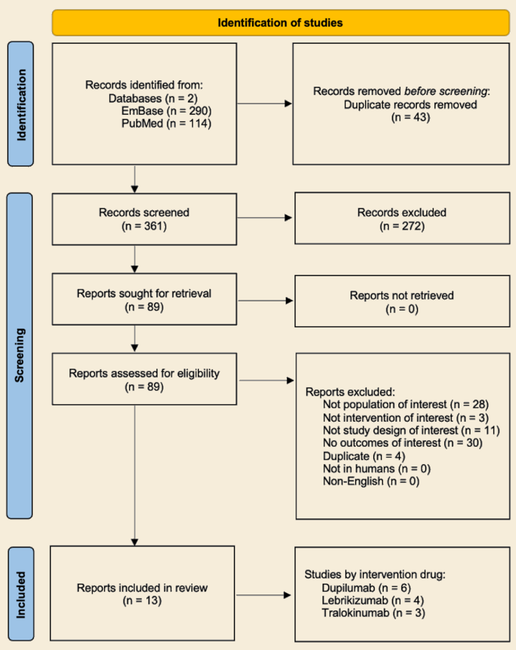


Table 2: Baseline Characteristics Across Included Studies[4-7]

NCT	Study Name	Geography	Intervention	Sample Size	Age (year), mean (SD)	Male Sex, %	Race, %	BMI, mean (SD)	Prior Systemic Treatment, %	AD Duration (year), mean (SD)	IGA Score, %	EASI, mean (SD)	Affected BSA (%), mean (SD)	SCORAD Score, mean (SD)	Pruritus NRS Score, %
NCT04146363 NCT04178967	ADvocate1 ADvocate2	Global	Lebrikizumab 250 mg Q2W	67	14.4 (1.6)	43.3	White: 55.2 Asian: 25.4 Black: 11.9	25.1 (7.2)	47.8	11.2 (4.6)	3: 61.2 4: 38.8	29.2 (11.0)	44.7 (21.0)	64.2 (11.4)	<4: 11.1 ≥4: 88.9
			Placebo Q2W	35	15.0 (1.7)	42.9	White: 68.6 Asian: 25.7 Black: 5.7	24.8 (5.8)	45.7	12.0 (4.3)	3: 68.6 4: 31.4	28.8 (12.1)	42.9 (24.3)	66.0 (10.4)	<4: 11.8 ≥4: 88.2
NCT03526861	ECZTRA 6	Global	Tralokinumab 300 mg Q2W	97	14.6	48.5	White: 57.7 Asian: 20.6 Black: 14.4 Hispanic: 9.3	NR	53.6 (55.7)	12.1 (3.5)	4: 49.5	31.8 (13.9)	49.6 (23.3)	68.3 (13.7)	NR
			Tralokinumab 150 mg Q2W	98	14.8	52	White: 56.1 Asian: 28.6 Black: 7.1 Hispanic: 10.2	NR	71.4 (73.4)	12.1 (3.7)	4: 44.9	32.1 (12.9)	52.4 (22.6)	67.7 (14.4)	NR
			Placebo Q2W	94	14.3	54.3	White: 56.4 Asian: 24.5 Black: 11.7 Hispanic: 6.4	NR	73.4 (76.6)	12.7 (3.7)	4: 45.7	31.2 (14.5)	51.4 (23.9)	67.4 (14.9)	NR
NCT03054428	AD ADOL	United States & Canada	Dupilumab 300 mg Q4W	84	14.4 (1.6)	61.9	White: 65.5 Asian: 15.5 Black: 9.5	24.1 (5.9)	45.8	11.9 (3.2)	3: 45.2 4: 54.8	35.8 (14.8)	56.9 (23.5)	69.8 (14.1)	7.5 (1.8)*
			Dupilumab 200/300 mg Q2W	82	14.5 (1.7)	52.4	White: 65.9 Asian: 14.6 Black: 8.5	24.9 (7.9)	42.7	12.5 (3.0)	3: 47.6 4: 52.4	35.3 (13.8)	56.0 (21.4)	70.6 (13.9)	7.5 (1.5)*
			Placebo Q2W	85	14.5 (1.8)	62.4	White: 56.5 Asian: 15.3 Black: 17.6	23.9 (6.0)	38.8	12.3 (3.4)	3: 45.9 4: 54.1	35.5 (14.0)	56.4 (24.1)	70.4 (13.3)	7.7 (1.6)*

*Peak pruritis NRS score, mean (SD)
AD = atopic dermatitis; BMI = body mass index; BSA = body surface area; EASI-75 = 75% Improvement from Baseline in Eczema Area and Severity Index Score (0-72 scale: 0 = clear; 50.1-72 = very severe AD); IGA = Investigator's Global Assessment (0-4 scale: 3 = moderate; 4 = severe); NCT = national clinical trial; NRS = Numerical Rating Scale (0-10 scale: 0 = no itch; 10 = worst itch imaginable); SCORAD = Scoring Atopic Dermatitis (0-103 scale: <25 = mild; 25-50 = moderate; >50 = severe)

TAKEAWAYS

Dupilumab is the most efficacious biologic treatment for AD in adolescents in achieving EASI-75 and IGA Score 0/1 across 16 weeks of therapy, albeit with high uncertainty.

The relative effects estimates can serve as **evidence** to inform treatment decisions, medical policies, and future clinical guidelines.

Future studies, ideally **head-to-head trials**, are needed to further confirm these results. **JAK inhibitors** should be considered as well.

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CONTACT INFO

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