Efficacy Comparison of Targeted Systemic Monotherapies Including Lebrikizumab for Moderate-to-Severe Atopic Dermatitis: a Network Meta-Analysis

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BACKGROUND

- Atopic dermatitis (AD) is a chronic inflammatory skin disease affecting 2–7% of adults globally,[1] with 30% experiencing moderate-to-severe disease[2]
- Treatments for moderate-to-severe AD include biologics (e.g., dupilumab, tralokinumab, and lebrikizumab) and Janus kinase (JAK) inhibitors (e.g., abrocitinib, upadacitinib, and baricitinib)[3,4]
- However, the efficacy of many treatments has not been compared in head-to-head trials

OBJECTIVE

- To evaluate the relative efficacy between lebrikizumab, an emerging biologic, and approved targeted systemic AD treatments using a network meta-analysis (NMA)

KEY RESULTS

Figure 2. IGA 0/1 Absolute Response Rate Estimates (Baseline-Risk Adjusted RE model)

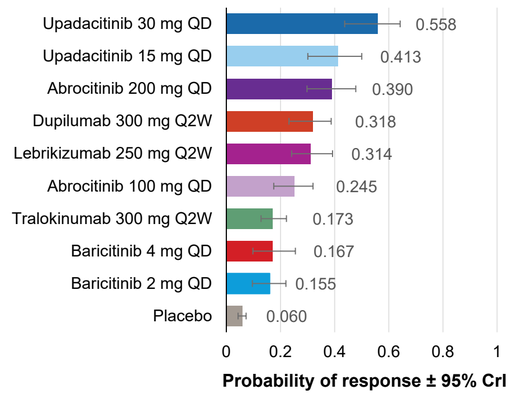
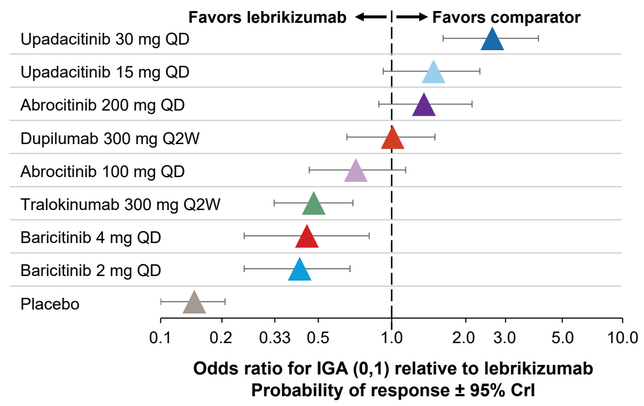


Figure 3. Odds Ratios for IGA 0/1 Relative to Lebrikizumab (Baseline-Risk Adjusted RE model)



LIMITATIONS

- Clinical trials were conducted at different timepoints and may have influenced the results
  - Efficacy outcomes for abrocitinib were assessed at 12 weeks rather than 16 weeks
- Absolute response estimates were influenced by placebo responses
- Slight differences in the IGA scales used between studies may have influenced the results
- The exact itch scale used in the clinical trials varied. However, the concept of itch measured by each of the scales was the same and for the comparison in the NMA they have been pooled together into one endpoint
- This NMA focused on a short treatment period of 16 weeks

CONCLUSIONS

- This 16-week NMA shows that lebrikizumab had a similar response rate to dupilumab, the most widely used targeted systemic therapy for AD, and, if approved, may represent a valuable treatment option for moderate-to-severe AD

METHODS

Study Design

- The NMA was based on the results of a systematic literature review and included randomized clinical trials of targeted systemic therapies (monotherapy-only, published before April 2023), before any treatment switch:
  - Abrocitinib, baricitinib, dupilumab, lebrikizumab, tralokinumab, and upadacitinib
- Studies with a high proportion of patients that withdrew consent or that were terminated prematurely were excluded
- Population: Adults (≥18 years) and adolescents (≥12 to <18 years) with moderate-to-severe AD
- Time range of interest: 4–16 weeks

Outcome Assessments

- Eczema Area and Severity Index (EASI): ≥50%, ≥70%, and ≥90% improvement in EASI scores from baseline:
  - EASI-50, EASI-75, and EASI-90
- Investigator's Global Assessment (IGA) of 0 (clear) or 1 (almost clear)
- Pruritus Numeric Rating Scale (NRS): ≥4-point improvement from baseline[5]

Statistical Analysis

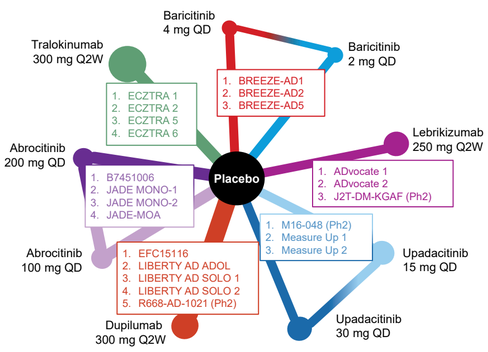
- As recommended for decision-making based on evidence synthesis analyses, Bayesian methods were used to conduct analyses[6]
- Baseline risk-adjusted models were preferred over unadjusted models if the baseline risk coefficient was statistically significant, indicated by a credible interval (CrI) that does not contain zero
- Both fixed and random-effects (RE) models were fitted. The RE model was preferred unless the fixed effects model had a decisively better fit, indicated by a deviance information criterion of ≥5 points[7]
- Analyses of all endpoints used non-response imputation methodology
- Meta-regression was performed to adjust for baseline severity in analysis of EASI & IGA outcomes
- Risk of bias was evaluated using The Cochrane Collaboration's Risk of Bias Assessment Tool,[8] and NMA feasibility assessments were performed for each outcome of interest

RESULTS

NMA Results

- The NMA analyzed 22 phase II and III randomized clinical trials of targeted systemic therapies which used the approved dosing schemes (**Figure 1**)

Figure 1. Network Meta-Analysis Diagram



For each intervention, line weightings denote the number of studies and node weightings denote the number of patients. List of studies included in the NMA: Abrocitinib (100mg and 200mg): NCT02780167, NCT03349060, NCT03575871, and NCT03915496. Baricitinib (2mg and 4mg): NCT03334396, NCT03334422, and NCT03435081. Dupilumab 300mg, NCT03912259, NCT03054428, NCT02277743, NCT02277769, and NCT01859988. Lebrikizumab 250mg: NCT04146363, NCT04178967, and NCT03443024. Tralokinumab 300mg: NCT03131648, NCT03160885, NCT03562377, and NCT03526861. Upadacitinib (15mg and 30mg), NCT02925117, NCT03569293, and NCT03607422.

- Goodness-of-fit statistics supported the baseline risk-adjusted RE model to analyze all outcomes
- The estimated treatment effect did not depend on baseline severity for either EASI or IGA outcomes. This was determined through a meta-regression model which included a term that modelled the relationship between baseline severity and treatment (i.e., an interaction) in the model, however, this did not decisively improve model fit
- All targeted systemic monotherapies for AD were more efficacious than placebo for all outcomes
- At 12–16 weeks, the estimated response rates for the efficacy outcomes of EASI (50/75/90) and IGA 0/1 were most favorable for upadacitinib (30mg QD and 15mg QD)
- Lebrikizumab 250 mg Q2W had higher estimates for IGA 0/1 (**Figure 2**), EASI (50/75/90) (**Figure 4**), and lower number needed to treat (NNT) (**Table 1**) compared to abrocitinib 100mg QD, tralokinumab 300mg Q2W, and baricitinib (2mg QD and 4mg QD)
- The IGA 0/1 estimates for lebrikizumab 250mg Q2W were statistically comparable to dupilumab 300mg Q2W, the most widely used treatment for AD (**Figure 2**)
- **Figure 3** shows the odds of achieving an IGA 0/1 response for all treatments versus lebrikizumab 250mg Q2W
  - CrIs for abrocitinib (100mg QD and 200mg QD), dupilumab 300 mg Q2W, and upadacitinib 15mg QD overlapped with lebrikizumab 250mg Q2W, indicating that their IGA 0/1 response rates were not statistically different

Figure 4. EASI-50, EASI-75, and EASI-90 Absolute Response Rate Estimates (Baseline-Risk Adjusted RE model)

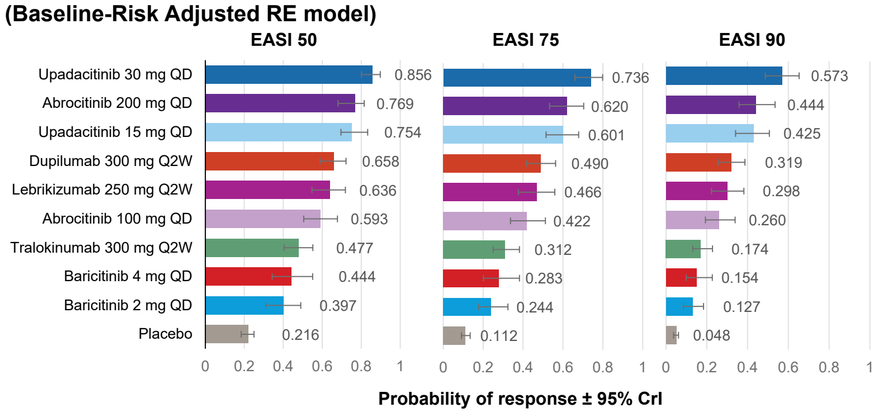
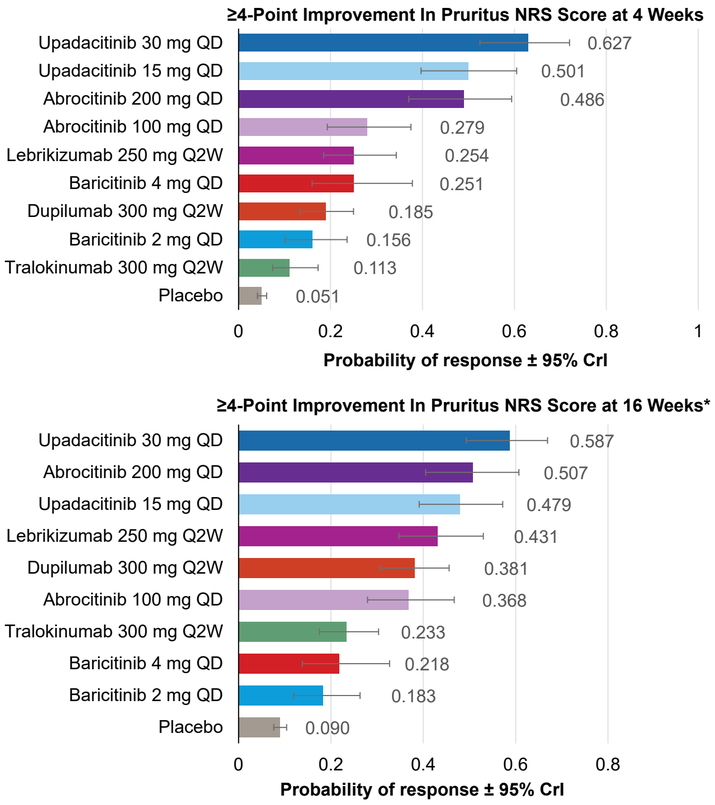


Table 1. Number Needed to Treat (Baseline-Risk Adjusted RE model)

Treatment	EASI-50 95% CrI	EASI-75 95% CrI	EASI-90 95% CrI	IGA 0/1 95% CrI	NRS ≥4 Week 4 95% CrI	NRS ≥4 week 16 95% CrI
Upadacitinib 30 mg QD	1.565 (1.476, 1.686)	1.604 (1.473, 1.795)	1.907 (1.670, 2.253)	2.011 (1.735, 2.566)	1.735 (1.501, 2.091)	2.014 (1.737, 2.446)
Upadacitinib 15 mg QD	1.859 (1.696, 2.104)	2.044 (1.794, 2.426)	2.656 (2.209, 3.349)	2.836 (2.303, 3.947)	2.223 (1.814, 2.856)	2.572 (2.088, 3.265)
Abrocitinib 200 mg QD	1.809 (1.641, 2.039)	1.970 (1.713, 2.329)	2.529 (2.075, 3.182)	3.035 (2.414, 4.050)	2.299 (1.847, 3.124)	2.395 (1.941, 3.159)
Dupilumab 300 mg Q2W	2.263 (2.026, 2.588)	2.642 (2.273, 3.159)	3.694 (3.017, 4.667)	3.885 (3.114, 5.456)	7.450 (5.098, 11.770)	3.437 (2.765, 4.496)
Lebrikizumab 250 mg Q2W	2.382 (2.030, 2.928)	2.819 (2.282, 3.661)	4.005 (3.038, 5.561)	3.932 (3.041, 5.327)	4.917 (3.420, 7.390)	2.928 (2.278, 3.861)
Abrocitinib 100 mg QD	2.653 (2.215, 3.332)	3.223 (2.557, 4.273)	4.716 (3.509, 6.678)	5.415 (3.897, 8.121)	4.382 (3.102, 7.001)	3.591 (2.665, 5.276)
Tralokinumab 300 mg Q2W	3.836 (3.096, 4.962)	4.995 (3.846, 6.761)	7.917 (5.760, 11.320)	8.822 (6.361, 13.030)	16.090 (8.327, 39.130)	6.990 (4.779, 11.090)
Baricitinib 4 mg QD	4.383 (3.059, 7.398)	5.821 (3.806, 10.430)	9.432 (5.711, 18.150)	9.346 (5.278, 21.090)	4.988 (3.072, 8.928)	7.834 (4.292, 18.970)
Baricitinib 2 mg QD	5.524 (3.799, 9.611)	7.550 (4.905, 13.860)	12.630 (7.668, 24.700)	10.540 (6.493, 21.470)	9.509 (5.454, 18.820)	10.760 (5.927, 28.770)

- **Figure 5** shows the Pruritus NRS response rates for all treatments at weeks 4 and 16
  - Lebrikizumab 250mg Q2W had higher Pruritus NRS response rates among all biologics
  - Lebrikizumab 250mg Q2W had more favorable Pruritus NRS response rates compared to JAK inhibitors baricitinib 2mg QD and abrocitinib 100mg QD

Figure 5. Pruritus NRS at Weeks 4 and 16* After Treatment (Baseline-Risk Adjusted RE model)



*Primary endpoint timepoint was ≥4-Point improvement in the Pruritus NRS score between baseline and Week 16.

ABBREVIATIONS: AD, atopic dermatitis; CrI, credible interval; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; NNT, number needed to treat; NRS, Numeric Rating Scale; NMA, network meta-analysis; Ph2, phase 2; Q2W, once every 2 weeks; QD, once daily; RE, random-effects.

REFERENCES

1. Avena-Woods, C. *Am J Manag Care*. 2017;23(8 Suppl): S115-s123. **2.** Barbarot, S., et al. *Allergy*. 2018;73(6): 1284-1293. **3.** Newsom, M., et al. *Drugs*. 2020;80(11): 1041-1052. **4.** Ständer S. *N Engl J Med*. 2021;384:1136–43. **5.** Revolutionizing Atopic Dermatitis, 11-13 December 2021. *Br J Dermatol*. 2022;186(4):e135-e185. **6.** Dias, S., et al. Technical Support Document in Evidence Synthesis. 2011: National Institute for Health and Clinical Excellence. **7.** Spiegelhalter, D. J., et al. *J Royal Statistical Society*. 2002;64(4):583-616. **8.** Higgins JP., et al. *BMJ*. 2011;343: d5928.

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