Comparison of Efficacy of Targeted Therapies without Topical Corticosteroids for Moderate to Severe Atopic Dermatitis: Systematic Review and Network Meta-analysis

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Introduction: Targeted therapies for patients with moderate to severe atopic dermatitis (AD) have been recently evaluated in multiple randomized controlled trials (RCTs), but comparative efficacy evidence among these therapies is lacking. Reported here are network meta-analysis (NMA) results comparing efficacy measures of skin clearance and itch among targeted therapies as monotherapy without concomitant topical corticosteroids (TCS).

Methods: We conducted a systematic literature review (SLR) that searched the Cochrane Central Register of Controlled Trials, MEDLINE, Embase, Latin American and Caribbean Health Science Information database, Global Resource of Eczema Trials database, and clinical trial registries in October 2020. English-language RCTs (phase III and IV) with ≥8 weeks of systemic immunomodulatory treatment for moderate to severe AD were included. Data from two upadacitinib trials (Measure Up 1 [NCT03569293], Measure Up 2 [NCT03607422]) were also included. The SLR adhered to Preferred Reporting Items for Systematic Reviews and Meta-analyses for Network Meta-Analyses guidelines. Prespecified efficacy outcomes were: Investigator Global Assessment score of 0 or 1 (clear or almost clear) with a ≥2-point reduction from baseline (IGA 0/1), ≥75% and ≥90% improvement in Eczema Area and Severity Index (EASI) from baseline (EASI-75, EASI-90), and ≥4-point improvement in Pruritus Numerical Rating Scale from baseline (ΔNRS≥4). Bayesian NMA was performed for each outcome evaluated at the primary endpoint timepoint of each trial (week 12 for abrocitinib, week 16 for all other therapies). Fixed-effect, random-effect, and baseline risk-adjusted model fit statistics and diagnostics were evaluated to select the best fitting models. Odds ratio (OR), number needed-to-treat (NNT), placebo-unadjusted absolute response rate (ARR), and surface under the cumulative ranking curve (SUCRA) scores were estimated. Statistical significance among therapies was assessed by OR 95% credible intervals excluding 1.

Results: Of 2,553 unique records identified in the SLR, 282 publications were assessed for eligibility. A total of six records representing nine unique studies were extracted. When including the upadacitinib trials, the NMA analyzed 11 unique placebo-controlled trials
encompassing 6,254 patients in 28 arms across five targeted therapies (abrocitinib, baricitinib, dupilumab, tralokinumab, upadacitinib). Fit statistics and diagnostics supported fixed-effect models for all outcomes analyzed. For each outcome, all targeted therapies had OR estimates that were significantly different from placebo. For IGA 0/1, OR and NNT versus placebo, ARR, and SUCRA score were most favorable for upadacitinib 30mg (OR=19.5, NNT=1.9, ARR=59.9%, SUCRA=99.9%), followed by upadacitinib 15mg (OR=11.1, NNT=2.6, ARR=46.0%, SUCRA=85.3%), abrocitinib 200mg (OR=7.7, NNT=3.4, ARR=37.2%, SUCRA=73.3%), and dupilumab (OR=5.7, NNT=4.3, ARR=30.6%, SUCRA=60.3%), with upadacitinib 30mg demonstrating significant differences versus all other therapies based on OR. For EASI-75, estimates were also most favorable for upadacitinib 30mg (OR=19.1, NNT=1.7, ARR=70.4%, SUCRA=98.3%), followed by abrocitinib 200mg (OR=13.3, NNT=2.0, ARR=62.4%, SUCRA=85.8%), upadacitinib 15mg (OR=10.9, NNT=2.2, ARR=57.6%, SUCRA=77.9%), and dupilumab (OR=6.0, NNT=3.2, ARR=43.0%, SUCRA=55.6%). This rank ordering was consistent for EASI-90 (upadacitinib 30mg [OR=23.2, NNT=2.0, ARR=54.8%, SUCRA=98.4%]; abrocitinib 200mg [OR=13.5, NNT=2.8, ARR=41.5%, SUCRA=82.5%]; upadacitinib 15mg [OR=12.8, NNT=2.9, ARR=40.1%, SUCRA=79.8%]; dupilumab [OR=6.2, NNT=5.1, ARR=24.5%, SUCRA=50.2%]) and ∆NRS≥4 (upadacitinib 30mg [OR=12.9, NNT=2.2, ARR=55.2%, SUCRA=98.9%]; abrocitinib 200mg [OR=8.3, NNT=2.8, ARR=44.3%, SUCRA=82.3%]; upadacitinib 15mg [OR=7.6, NNT=3.0, ARR=42.0%, SUCRA=77.7%]; dupilumab [OR=5.2, NNT=4.1, ARR=33.0%, SUCRA=54.7%]).

**Conclusion:** Among targeted therapies used as monotherapy without concomitant TCS, upadacitinib 30mg appears to be the most efficacious treatment for patients with moderate to severe AD, followed by abrocitinib 200mg, upadacitinib 15mg, and dupilumab.

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