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Comparative Effectiveness of Ruxolitinib Cream Versus Conventional Systemic Immunosuppressants in Moderate Atopic Dermatitis: A Target Trial Emulation Using A-STAR

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Introduction

- Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease[1]
  - Moderate disease is common and imposes considerable quality-of-life, work-productivity, and economic burden
- Guidelines for AD recommend the following stepwise pathway: emollients, topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI), phototherapy, conventional systemic immunosuppressants, and advanced systemics (biologics, oral Janus kinase inhibitors [JAKi])[2,3]
- Despite guideline-directed topical therapy, 30%–50% of patients with moderate AD report uncontrolled disease and ~30% report treatment dissatisfaction, frequently prompting escalation to systemic therapy[1,4]
- Conventional systemic immunosuppressants, principally methotrexate (MTX) and ciclosporin (CsA), are frequently used off-label in moderate AD before escalation to biologics and oral JAKi[2,3,5,6]
- Ruxolitinib (selective JAK1/JAK2 inhibitor) cream (1.5%) demonstrated efficacy in adults with moderate AD who had an inadequate response, intolerance, or contraindication to TCS and TCI in TRuE-AD4 (NCT06238817), and thus may be an alternative before escalation to conventional systemic immunosuppressants[7]
- No head-to-head randomized evidence compares ruxolitinib cream with conventional systemic immunosuppressants, and no suitable common comparator was identified to support an anchored indirect comparison

Objective

- To estimate the comparative effectiveness of 1.5% ruxolitinib cream versus conventional systemic immunosuppressants in adults with moderate AD for whom TCS and TCI are inadequate or inappropriate using a target trial emulation with a registry-based external control arm (ECA)

Methods

Study Design and Data Sources

- An active-comparator target trial emulation was conducted comparing patients applying ruxolitinib cream in TRuE-AD4 (n=160) with an ECA containing trial-eligible patients receiving conventional systemics (MTX and CsA) from the UK–Irish Atopic eczema Systemic TherApy Register (A-STAR; 46 UK sites; data cut-off January 26, 2026)[8-10]
- Time zero, eligibility criteria, treatment and outcome definitions, end of follow-up, and the handling of intercurrent events and missing data were aligned across sources
  - The design followed the National Institute for Health and Care Excellence (NICE) real-world evidence framework and was pre-specified in a protocol–statistical analysis plan[11]

Population, Comparators, and Outcomes

- ECA was derived based on TRuE-AD4 eligibility criteria and included age (≥18 y), AD duration (>2 y), baseline severity (Eczema Area and Severity Index [EASI] >6, Dermatology Life Quality Index [DLQI] >9, itch numerical rating scale [NRS] ≥3), treatment history (prior use of TCS/TCI, no history of JAKi failure), and history of alcoholism, drug addiction, malignancy, and immunocompromising conditions
- ECA time zero was the initiation of the first trial-eligible conventional systemic treatment line following A-STAR enrollment after a patient was identified as trial-eligible; a practice-based treatment strategy permitted concomitant topical therapy and short-term bridging therapy, reflecting routine care
  - The comparator was a basket of MTX and CsA; azathioprine and mycophenolate were considered non-standard practice and were therefore excluded
    - Analyses were also conducted versus MTX and CsA separately
- Week 16 outcomes were ≥75% improvement from baseline in EASI (EASI-75) and the composite EASI-50 plus ≥4-point improvement in DLQI (EASI-50+DLQI4)
  - ECA responses were ascertained within a 12- to 20-week window; missing responses were imputed as non-response in both arms, replicating the trial estimand

Statistical Analysis

- Confounders were pre-specified from structured UK clinical expert input combined with empirical prognostic modeling: age, sex, AD duration, baseline EASI, itch NRS, DLQI, and prior systemic therapy
- The primary estimand was the average treatment effect on the treated (ATT), estimated using doubly robust inverse probability of treatment weighted regression adjustment (IPWRA)[12]; overlap weighting was adopted in cases of poor overlap
  - Overlap and balance were assessed using covariate and propensity score distributions, effective sample sizes (ESS), and standardized mean differences (SMD) before and after weighting
- Pre-specified sensitivity analyses addressed alternative estimands and estimation methods, eligibility criteria, covariate sets, comparator definitions, index period (lines initiated from October 2022), baseline and response assessment windows, and complete case analysis; quantitative bias analysis used the E-value[13]
  - Unanchored matching-adjusted indirect comparisons (MAICs) against 2 published CsA cohorts provided external corroboration as additional sensitivity analysis[14,15]
    - The TRuE-AD4 population was reweighted to their aggregate baseline age, AD duration, itch NRS, and DLQI; baseline EASI could not be matched, as the trial and comparator severity distributions did not overlap

Results

Study Population and Composition of the Comparator Arm

- Applying TRuE-AD4 eligibility criteria to A-STAR identified 99 trial-eligible treatment lines; after excluding azathioprine and mycophenolate (5%), the ECA comprised 94 patients (MTX, n=68 [72.3%]; CsA, n=26 [27.7%])
  - 160 patients who applied ruxolitinib cream in TRuE-AD4 were also included
- CsA was most commonly initiated at 100 mg daily (73.1% on a stable regimen); MTX was initiated orally in 94.1% of the patients, most commonly at 10 or 15 mg weekly (60.3% on a stable regimen)
- Before weighting, ECA patients were younger (mean 31.8 vs 39.0 y), had longer AD duration, and markedly higher baseline EASI (21.0 vs 12.5); body mass index, sex, DLQI, and itch NRS were similar (**Table 1**)

Table 1. Baseline Characteristics by Treatment Arm Before and After ATT Weighting

Characteristic	Ruxolitinib cream (N=160)	Conventional systemics, unweighted (N=94)	Conventional systemics, ATT-weighted*
Age, mean (SD), y	39.0 (16.3)	31.8 (10.6)	35.0 (13.3)
Female, n (%)	86 (53.8)	51 (54.3)	61 (47.8)
BMI, mean (SD), kg/m^2	25.8 (4.7)	26.4 (5.2)	27.5 (5.1)
EASI, mean (SD)	12.5 (4.3)	21.0 (10.7)	11.8 (5.3)
Itch NRS, mean (SD)	7.6 (1.6)	7.9 (1.5)	7.9 (1.6)
DLQI, mean (SD)	19.3 (5.1)	18.9 (6.0)	19.5 (5.7)
Time since AD onset, mean (SD), mo	244.8 (177.4)	320.3 (142.3)	236.5 (153.7)
Prior use of TCI, n (%)	131 (81.9)	34 (36.2)	57 (45.0)
Prior use of any systemic therapy, n (%)	50 (31.2)	44 (46.8)	46 (35.9)

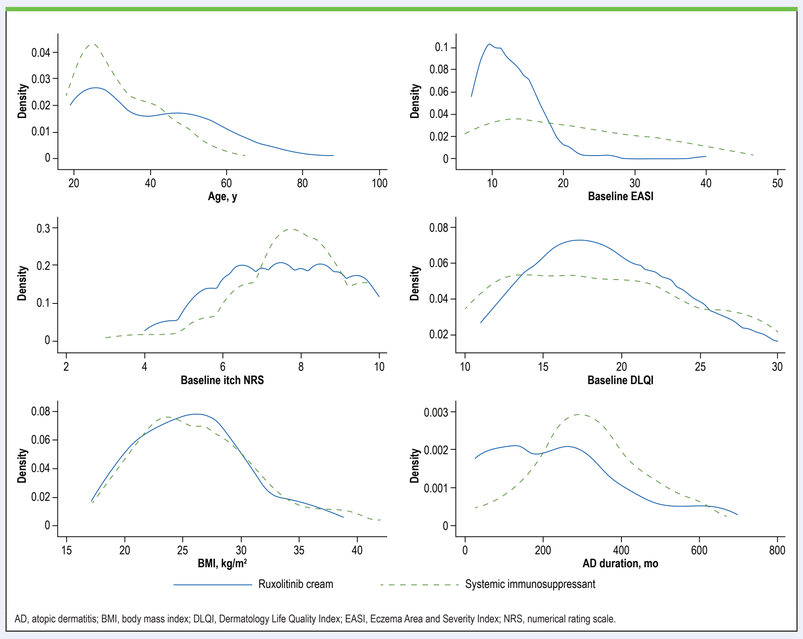
AD, atopic dermatitis; BMI, body mass index; ATT, average treatment effect on the treated; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; NRS, numerical rating scale; TCI, topical calcineurin inhibitor.
* Propensity score weighting targeting the ATT.

Results (Cont.)

Overlap and Balance

- Covariate and propensity score distributions indicated moderate overlap
  - Trial patients were clustered in the moderate EASI range at high propensity scores, whereas ECA patients spanned the severity distribution and clustered at lower propensity scores (**Figures 1** and **2**)
- A small number of large weights (**Figure 2B**) reduced the effective sample size of the ECA from 94 to 26 following ATT propensity score weighting; the ruxolitinib cream arm remained unweighted (n=160)
- Although propensity score weighting improved balance, SMDs remained >0.1 for age, sex, and itch NRS; thus, the regression component of IPWRA was required to correct for residual imbalance (**Figure 3**)

Figure 1. Distribution of Continuous Covariates in the Ruxolitinib Cream (TRuE-AD4) and Basket Comparator (A-STAR) Arms



AD, atopic dermatitis; BMI, body mass index; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; NRS, numerical rating scale.

Figure 2. (A) Propensity Score and (B) Weight Distributions: Ruxolitinib Cream Versus the Basket Comparator

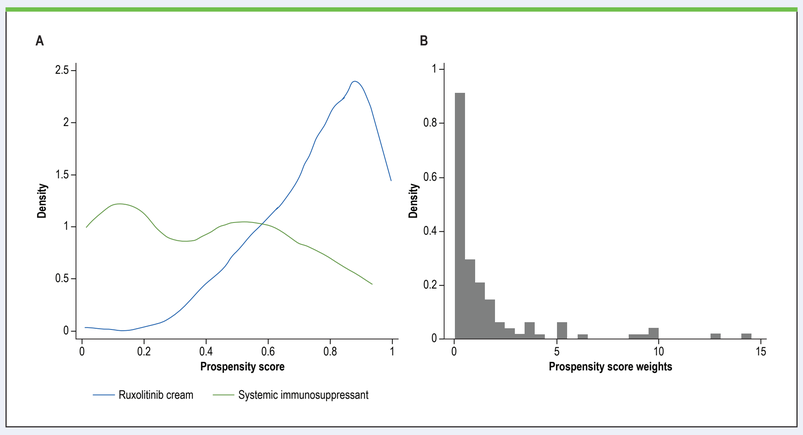
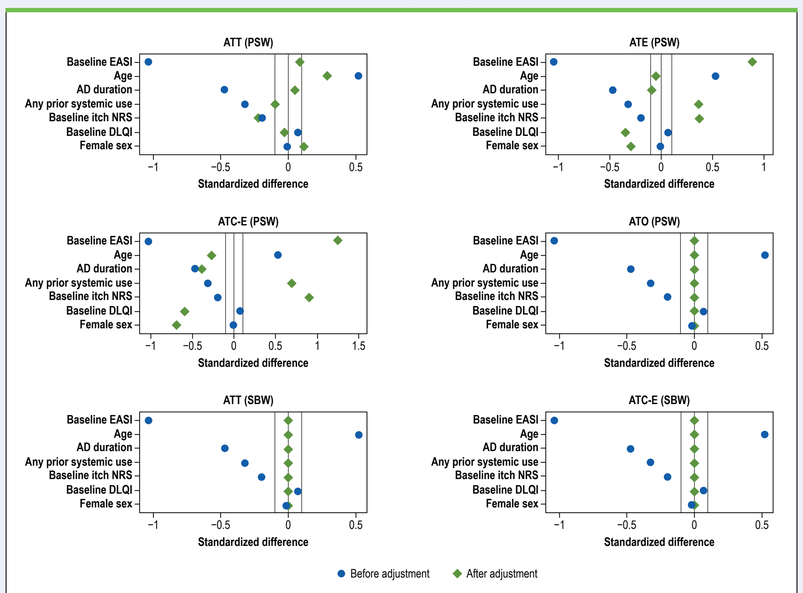


Figure 3. Standardized Differences in Baseline Characteristics by Treatment Arm Before and After Weighting



Each panel shows one estimand and adjustment method combination: propensity score weighting targeting the ATT, ATE, ATC-E and ATO, and stable balance weighting targeting the ATT and ATC-E. Standardized mean differences are displayed for baseline characteristics before weighting (circles) and after weighting (diamonds). Vertical lines represent the standard balance thresholds of ±0.1. Negative values indicate a lower mean in the ruxolitinib cream arm.
AD, atopic dermatitis; ATC-E, average treatment effect in the trial-eligible control population; ATE, average treatment effect; ATO, average treatment effect in the overlap population; ATT, average treatment effect on the treated; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; NRS, numerical rating scale; PSW, propensity score weighting; SBW, stable balance weighting.

Week 16 Response

- EASI-75 was achieved by 70.0% of ruxolitinib cream patients versus 18.1% on conventional systemics (unadjusted risk difference [RD], 0.519 [95% CI, 0.414–0.625]; **Table 2**)
- Adjustment increased rather than attenuated the effect (base-case IPWRA ATT RD, 0.577 [95% CI, 0.476–0.679]), consistent with the higher baseline EASI in the ECA, from which relative improvement is more readily achieved; the weighted comparator response fell to 12.3% (**Table 2**)
- EASI-50+DLQI4 was achieved by 78.8% of ruxolitinib cream patients versus 22.3% on conventional systemics (unadjusted RD, 0.564 [95% CI, 0.458–0.670]; adjusted RD, 0.655 [95% CI, 0.557–0.754]; **Table 2**)
- Against MTX, the adjusted EASI-75 RD using IPWRA was 0.586 (95% CI, 0.486–0.686), and against CsA, overlap was poor because these patients were more severe at baseline; IPWRA did not converge, and overlap weighting gave an RD of 0.433 (95% CI, 0.156–0.711; **Table 2**)
- The base-case EASI-75 risk ratio was 5.71 (95% CI, 3.10–10.51), corresponding to an E-value of 10.90 (5.65 for the confidence limit closest to the null)
  - Quantitative bias analysis indicated that the estimated EASI-75 benefit in favor of ruxolitinib cream was robust to unmeasured confounding. To fully explain away the observed association, an unmeasured baseline confounder would need to be associated with both treatment assignment and EASI-75 response by risk ratios of 10.90 each on an equal-strength basis and conditional on measured covariates. For context, the strongest measured covariate–response association had a risk ratio of 1.16

Table 2. Week 16 Response Rates and Risk Differences

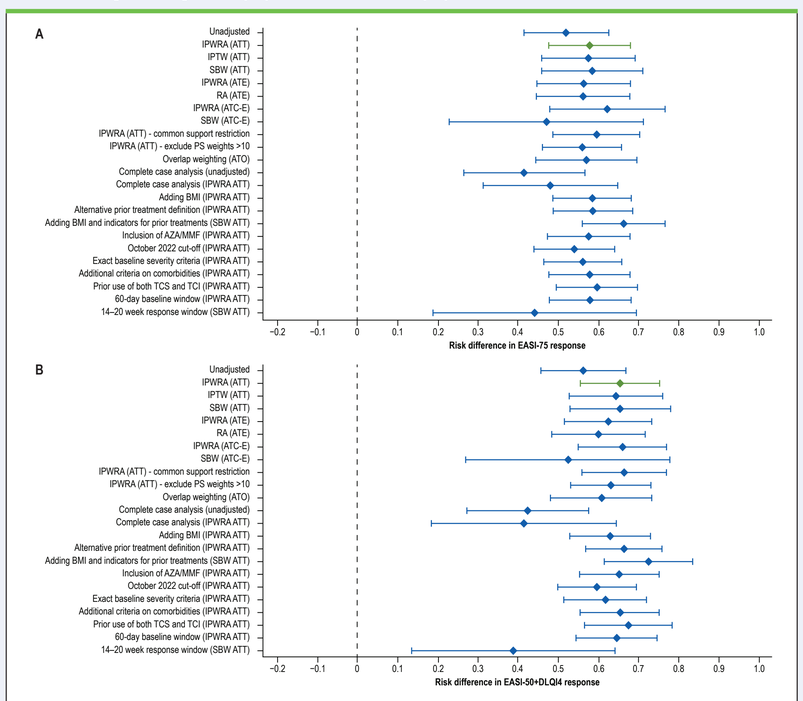
Endpoint	Comparator	Unadjusted response, %	Unadjusted RD (95% CI)	Adjusted RD (95% CI)
EASI-75 (ruxolitinib cream, 70.0%)	Conventional systemics (basket)	18.1	0.519 (0.414–0.625)	0.577 (0.476–0.679)
	Methotrexate	16.2	0.538 (0.425–0.651)	0.586 (0.486–0.686)
	CsA	23.1	0.469 (0.292–0.647)	0.433 (0.156–0.711)*
EASI-50+DLQI4 (ruxolitinib cream, 78.8%)	Conventional systemics (basket)	22.3	0.564 (0.458–0.670)	0.655 (0.557–0.754)
	Methotrexate	22.1	0.567 (0.449–0.684)	0.650 (0.549–0.751)
	CsA	23.1	0.557 (0.382–0.731)	0.587 (0.339–0.834)*

CsA, ciclosporin; DLQI4, ≥4-point improvement in Dermatology Life Quality Index score from baseline; EASI-50/75, ≥50%/≥75% improvement in Eczema Area and Severity Index score from baseline; IPWRA, inverse probability of treatment weighted regression adjustment; RD, risk difference.
* Overlap weighting; IPWRA did not converge versus ciclosporin owing to poor overlap.

Sensitivity analyses

- Estimates were stable across alternative estimands, estimation methods, eligibility criteria, covariate sets, comparator definitions and assessment windows, and in lines initiated from October 2022 onwards, indicating limited calendar-time bias (**Figure 4**)
- Exploratory MAICs versus published CsA cohorts gave EASI-75 risk differences of 0.508 (95% CI, 0.406–0.609; ESS, 73) and 0.462 (95% CI, 0.361–0.564; ESS, 124), consistent in magnitude with the A-STAR estimate versus CsA (0.433) and providing external corroboration of the registry-based findings

Figure 4. Adjusted Risk Difference in Response in Base-Case and Sensitivity Analysis: (A) EASI-75 and (B) EASI-50+DLQI4



Points are risk differences and horizontal lines are 95% confidence intervals; the base-case IPWRA estimate of the ATT is highlighted.
Baseline characteristics were measured over a pre-index window in TRuE-AD4 and the ECA in the base-case analysis (28 d and 30 d, respectively) with expansion to a longer pre-index window in the sensitivity analysis (60 d).
ATC-E, average treatment effect in the trial-eligible control population; ATE, average treatment effect; ATO, average treatment effect in the overlap population; ATT, average treatment effect in the treated population; AZA, azathioprine; MMF, mycophenolate mofetil; BMI, body mass index; DLQI4, ≥4-point improvement from baseline in Dermatology Life Quality Index; EASI-50, ≥50% improvement in Eczema Area and Severity Index score from baseline; EASI-75, ≥75% improvement in Eczema Area and Severity Index score from baseline; IPWRA, inverse probability of treatment weighted regression adjustment; IPTW, inverse probability of treatment weighting; PS, propensity score; SBW, stable balance weighting; RA, regression adjustment; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

Limitations

- The comparison of ruxolitinib cream with conventional systemic immunosuppressants was unanchored
  - Unbiasedness requires that all prognostic and effect-modifying variables were measured and adjusted for; thus, residual confounding cannot be excluded
- The small ECA constrained the eligibility criteria and covariates that could be applied, although all criteria and covariates identified as prognostic by clinical experts and prognostic modeling in A-STAR were applied in either primary or sensitivity analysis, which did not significantly impact the results
- Poor overlap versus CsA required overlap weighting and reliance on the transportability of overlap population estimates
- Some criteria and covariates could only be operationalized in A-STAR using proxies, and missing outcome data were more frequent due to the lack of protocol-mandated visits in routine care
- The estimated effect was attenuated in the complete case analysis, yet remained large and statistically significant

Conclusions

- **In adults with moderate AD inadequately controlled by guideline-directed topical therapy, ruxolitinib cream was associated with substantially higher Week 16 response than conventional systemic immunosuppressants after adjustment for measured confounding**
- **Findings were directionally consistent against MTX and CsA individually and stable across an extensive set of pre-specified sensitivity analyses**
- **Adjustment for measured confounders increased rather than attenuated the benefit, and quantitative bias analysis indicated that substantial unmeasured confounding would be required to overturn the result**
- **Results support ruxolitinib cream as a non-systemic alternative in adults with moderate AD for whom conventional topical therapies are inadequate or inappropriate**

Disclosures

AT is an employee of Arrow Health Economics, which received funding from Incyte Corporation to conduct this study. JL is an employee of Incyte Biosciences UK Ltd and a shareholder of Incyte Corporation. NP is an employee of Incyte Biosciences International Sàrl and a shareholder of Incyte Corporation. RG received consultancy fees from Incyte Corporation to advise on this study.

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