



BRIEF REPORT

Indirect Treatment Comparison of Baricitinib versus Dupilumab in Adults with Moderate-to-Severe Atopic Dermatitis

Marjolein S. de Bruin-Weller · Esther Serra-Baldrich · Sebastien Barbarot ·
Susanne Grond · Christopher Schuster · Helmut Petto ·
Jean-Philippe Capron · Afaf Raibouaa · Thomas Werfel

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ABSTRACT

Introduction: Indirect treatment comparison was used to compare approved doses of baricitinib and dupilumab for treating adult patients with moderate-to-severe atopic dermatitis (AD) who are candidates for systemic therapy.

Methods: Baricitinib and dupilumab were compared (Bucher method) at weeks 4 and 16. Performance in combination with topical corticosteroids (TCS) was analyzed in patients with inadequate response or inadvisable to topical

therapies (population A) and cyclosporine (population B). Population A was additionally examined as monotherapy.

Results: For the Eczema Area and Severity Index (EASI) 75, baricitinib and dupilumab were similar. A ≥ 4 -point improvement in itch numerical rating scale (NRS) was significantly more likely with baricitinib 4 mg than dupilumab in population A as monotherapy (RR = 2.62, 95% CI 1.22, 5.61, $p = 0.013$) and in TCS combination at week 4. These differences were not significant by week 16. For the Dermatology Life Quality Index (DLQI), baricitinib 4 mg and dupilumab were similar on mean difference in change from baseline (MD_{cfb}), though some differences were seen between baricitinib 2 mg and dupilumab at week 16 for the population A monotherapy (MD_{cfb} = 2.05, 95% CI 0.53, 3.56, $p = 0.016$) and TCS combination therapy (MD_{cfb} = 2.48, 95% CI 0.46, 4.50, $p = 0.016$) groups, and in population B (MD_{cfb} = 3.38 95% CI 1.18, 5.58, $p = 0.003$).

Conclusions: Baricitinib potentially offers more rapid improvement in itch while providing similar efficacy on EASI75 and DLQI outcomes compared with dupilumab.

M. S. de Bruin-Weller (✉)
Department of Dermatology and Allergology,
University Medical Center, Utrecht, The
Netherlands
e-mail: m.s.debruin-weller@umcutrecht.nl

E. Serra-Baldrich
Department of Dermatology, Cutaneous Allergy
Unit, Hospital Sant Pau, Universitat Autònoma
Barcelona, Barcelona, Spain

S. Barbarot
Department of Dermatology, Nantes Université,
CHU Nantes, INRAE, UMR 1280 PhAN, 44000
Nantes, France

S. Grond · C. Schuster · H. Petto · J.-P. Capron ·
A. Raibouaa
Eli Lilly and Company, Indianapolis, IN, USA

T. Werfel
Division of Immunodermatology and Allergy
Research, Department of Dermatology and Allergy,
Hannover Medical School, Hannover, Germany

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Key Summary Points

Head-to-head (H2H) trial evidence regarding the performance of novel therapies versus their competitors is often lacking.

Indirect treatment comparisons (ITC) allow the results of existing trials to be compared in a rigorous way and can help to bridge knowledge gaps when H2H comparisons are not available.

Baricitinib represents an approved oral treatment option for adult patients with moderate-to-severe AD that offers similar efficacy on the Eczema Area and Severity Index (EASI)75 and Dermatology Life Quality Index (DLQI) to dupilumab when indirectly compared.

Baricitinib potentially offers more rapid improvement in itch, a key symptom for patients, than dupilumab when indirectly compared.

INTRODUCTION

Baricitinib, a selective Janus kinase (JAK)1/JAK2 inhibitor, is approved in several countries for the treatment of moderate-to-severe atopic dermatitis (AD) in adults who are candidates for systemic therapy [1]. It has proven effective both as monotherapy and in combination with topical corticosteroids (TCS) [2, 3].

At present, there are no existing head-to-head (H2H) trials comparing the efficacy of baricitinib with other approved systemic therapies available for the management of AD in this patient population. In such circumstances, methodological tools such as indirect treatment comparisons (ITC) are often employed by researchers [4, 5]. ITC methodologies use the results of direct comparisons with a common comparator, such as placebo (PBO), to evaluate the relative efficacy of different interventions.

To support physicians when choosing appropriate treatments for AD, we conducted an ITC across all approved systemic therapies for the treatment of moderate-to-severe AD in adults with PBO-controlled randomized controlled trial evidence.

METHODS

To identify relevant studies for our ITC, we systematically reviewed the literature for placebo-controlled trials evaluating systemic therapies in adults with moderate-to-severe AD over four waves starting in 2018 with updates in 2019, and May and December 2020. Eligibility criteria for the review were: studies in adults with confirmed moderate-to-severe AD; randomized controlled trials of a comparative investigation (one of which could be PBO); and studies published in English or German. We interrogated MEDLINE and Embase, both via Ovid Search Platform, and The Cochrane Central Register of Controlled Trials (CENTRAL) for published studies as well as ClinicalTrials.gov (<http://clinicaltrials.gov/>), the International Clinical Trials Registry Platform Search Portal, and the search portal of the World Health Organization to identify potentially relevant studies based on ongoing trials.

The only approved treatments with PBO-controlled trial data identified by the review at this time were dupilumab [6] and baricitinib. The approved dose of dupilumab (300 mg subcutaneously every 2 weeks following a loading dose of 600 mg) [7, 8] was then indirectly compared with baricitinib 2/4 mg once daily [1] using PBO as the common comparator (Fig. 1). When treatment data were available from more than one study versus PBO, standard meta-analysis methods were applied before conducting ITC by means of the Bucher methodology ITC [5].

Patient-level data were available for all baricitinib studies, whereas for dupilumab outcomes, data were extracted from the published literature. The ITC was conducted in two patient populations with subcohorts: population A and population B. Population A consisted

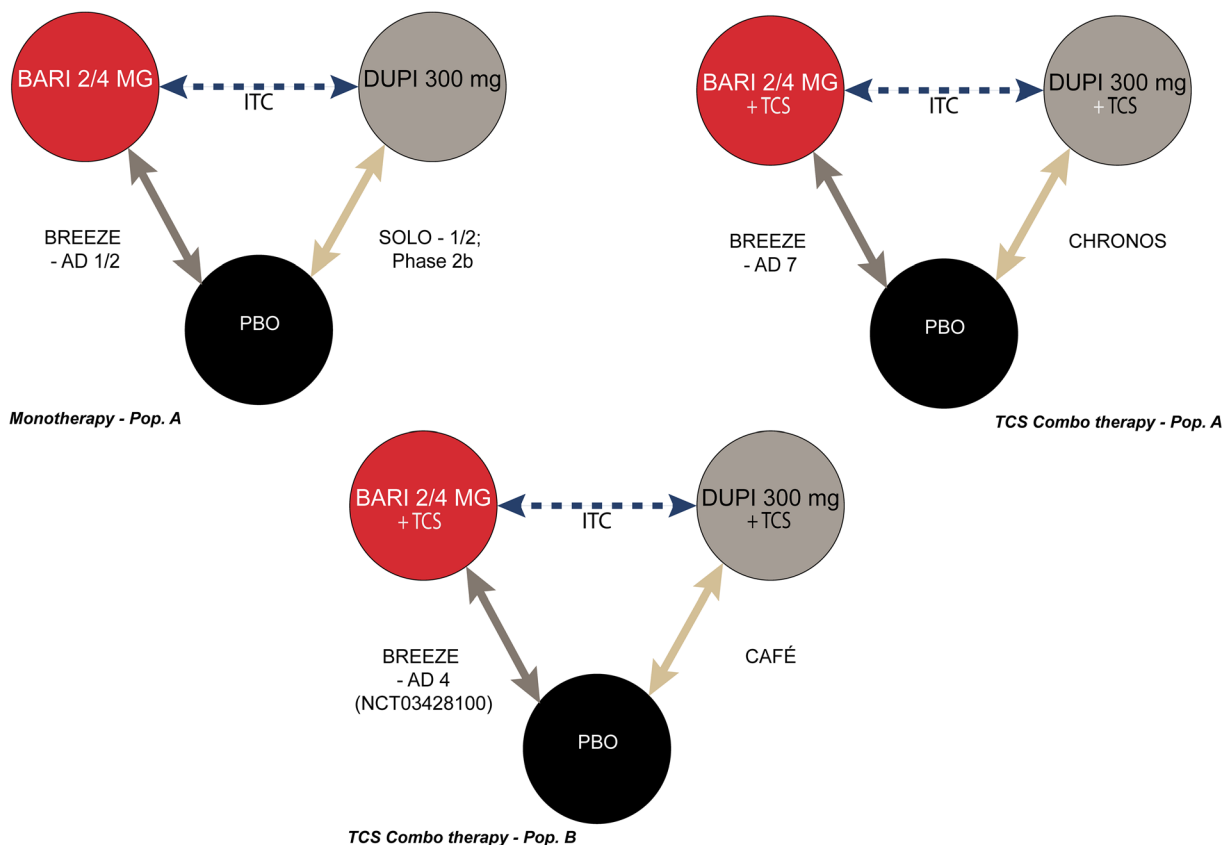


Fig. 1 Structure of ITC analysis of BARI 2/4 mg versus DUPI 300 mg Q2W. *BARI* baricitinib, *DUPI* dupilumab, *ITC* indirect treatment comparison, *QxW* every *x* weeks, *TCS* topical corticosteroids. Population A: patients who

were intolerant of, had contraindications to, or did not respond to topical treatments. Population B: patients who were also intolerant of, had contraindications to, or did not respond to, cyclosporine

of two cohorts, while population B included only one cohort:

Population A: patients who were intolerant of, had contraindications to, or did not respond to topical treatments

- Cohort 1: patients receiving baricitinib or dupilumab as monotherapy
- Cohort 2: patients receiving baricitinib or dupilumab in combination with TCS

Population B: patients who were also intolerant of, had contraindications to, or did not respond to cyclosporine:

- Cohort 1: patients receiving baricitinib or dupilumab in combination with TCS

The ITC was based on the relative efficacy (relative risk [RR]) of the two agents assessed

versus PBO for each of the binary outcomes. Where RRs were > 1, results favored baricitinib, while RRs < 1 favored dupilumab. For Dermatology Life Quality Index (DLQI) assessments, the ITC was based on mean difference in change from baseline (MDc_{fb}). MDc_{fb} > 0 favored dupilumab while MDc_{fb} < 0 favored baricitinib. An overview of the population groups is provided in Table 1.

Informed by the primary and key secondary endpoints common across the trials identified in the systematic literature review, we assessed the following efficacy outcomes in our study at week 4 and again at week 16: the proportion of patients with ≥ 75% improvement in Eczema Area and Severity Index (EASI75), the proportion of patients with ≥ 4-point improvement in itch Numeric Rating Scale (NRS) from baseline

Table 1 Relevant trials identified by systematic literature review

Patient population of adults with moderate-to-severe AD	BARI randomized clinical trials	DUPI randomized clinical trials
Population A: patients who had failed topical treatment, or had contraindication to or were intolerant of topical treatments	Monotherapy: BREEZE-AD1 [3] BREEZE-AD2 [3] TCS combination therapy: BREEZE-AD7 [4]	Monotherapy: SOLO-1 [21] SOLO-2 [10] Phase 2b [22] TCS combination therapy: CHRONOS [23]
Population B: patients who had inadequate response to existing topical medications and failed cyclosporine, or had contraindications to or were intolerant to cyclosporine	TCS combination therapy: BREEZE-AD4 (NCT03428100) [24]	TCS combination therapy: CAFÉ [25]

While we deemed a phase II trial of dupilumab to meet the inclusion criteria, a phase II trial of baricitinib had too small a sample size for inclusion

AD atopic dermatitis, BARI baricitinib, DLQI Dermatology Life Quality Index, DUPI dupilumab, TCS topical corticosteroid

(peak daily pruritus NRS score used as equivalent; both instruments measure worst level of itch within the past 24 h [9–11]), and change from baseline (CFB) in Dermatology Life Quality Index (DLQI).

Missing data were accounted for by non-responder imputation (NRI) for binary outcomes, while for the DLQI, least-squared means were selected from the relevant included studies. Patients in receipt of rescue treatment or who discontinued treatment were considered non-responders. Statistical analyses were conducted using the CHEETAH tool (Indirect Comparison on results from 2 Meta-Analyses version 1.1), a program developed by Eli Lilly based on the R package “meta” [12].

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

At the time of the systematic literature review (SLR), nine parallel PBO trials (four baricitinib and five dupilumab) covering 3364 patients were identified to inform the ITC (Table 1). Baseline characteristics for each of the trials are given in Table 2 and are consistent with comparable disease severity based on EASI, itch, and DLQI scores across all included studies. The results of the ITC analysis are summarized in Table 3. In population A at week 4, there was no significant difference between EASI75 response rates for either treatment group, though RR values numerically favored both baricitinib 2 and 4 mg. Similarly, at week 16 there was no statistically significant difference, though in this instance, RR values numerically favored dupilumab. This pattern was replicated in population B.

With respect to ≥ 4 -point improvement in itch NRS from baseline between baricitinib 2 or 4 mg and dupilumab in either monotherapy or TCS combination therapy studies at week 16, no

Table 2 Baseline characteristics of patients in monotherapy studies included in the ITC

Study	Molecule (therapy)	Baseline population pooled data ^{a,b} (n)	Age (years; mean) [SD]	Mean baseline scores (SD)		
				EASI	DLQI	Itch/ pruritis ^d NRS
BREEZE-AD1	BARI (Mono)	497	35.5 (13.3)	31.8 (12.8)	13.8 (7.3)	6.6 (2.1)
BREEZE-AD2	BARI (Mono)	490	35.0 (13.3)	33.5 (13.8)	14.5 (8.0)	6.7 (2.2)
BREEZE-AD7	BARI (Combi)	329	33.8 (12.5)	29.7 (12.3)	15.0 (7.8)	7.1 (1.9)
BREEZE-AD4	BARI (Combi)	370	38.0 (13.8)	31.5 (12.5)	13.9 (7.5)	6.8 (2.0)
SOLO 1	DUPI (Mono)	448	38.5 ^c	31.1 ^c	13.5 ^c	7.7 ^c
SOLO 2	DUPI (Mono)	469	34.5 ^c	29.6 (N/A)	15.0 (N/A)	7.8
Phase 2b trial	DUPI (Mono)	125	38.3 (12.6)	33.4 (14.2)	13.7 (6.7)	6.3 (1.8) ^c /6.5 (2.0)
CHRONOS	DUPI (Combi)	421	35.6 (N/A)	29.9 (N/A)	13.9 ^c	7.6 ^c
CAFÉ	DUPI (Combi)	215	38.2 (13.1)	33.1 (10.1)	13.5 ^c	6.5 (2.3)

N/A not applicable

^aPooled data for approved dosage regimens and placebo

^bIn BREEZE-AD1, patients were randomized to receive baricitinib 2 mg ($n = 123$), baricitinib 4 mg ($n = 125$), baricitinib 1 mg ($n = 127$; not included in pooled data), or placebo ($n = 249$); in BREEZE-AD2, patients were randomized to receive baricitinib 2 mg ($n = 123$), baricitinib 4 mg ($n = 123$), baricitinib 1 mg ($n = 125$; not included in pooled data), or placebo ($n = 244$). In BREEZE-AD4, all patients received TCS and were randomized to baricitinib 2 mg ($n = 185$), baricitinib 4 mg ($n = 92$), baricitinib 1 mg ($n = 93$; not included in pooled data), or placebo ($n = 93$); in BREEZE-AD7, all patients received TCS and were randomized to baricitinib 2 mg ($n = 109$), baricitinib 4 mg ($n = 111$), or placebo ($n = 109$). In SOLO 1, patients were randomized to receive dupilumab 300 mg Q2W ($n = 224$), dupilumab 300 mg Q1W ($n = 223$; not included in pooled data), or placebo ($n = 224$); in SOLO 2, patients were randomized to receive dupilumab 300 mg Q2W ($n = 233$), dupilumab 300 mg Q1W ($n = 239$; not included in pooled data), or placebo ($n = 236$); in the phase 2b trial, patients were randomized to receive dupilumab 300 mg Q2W ($n = 64$), placebo ($n = 61$), or other regimens not included in pooled data: dupilumab 100 mg Q4W ($n = 65$), dupilumab 300 mg Q4W ($n = 65$), dupilumab 300 mg Q1W ($n = 63$), or dupilumab 200 mg Q2W ($n = 61$). In CHRONOS, all patients received TCS and were randomized to dupilumab 300 mg Q2W ($n = 106$), dupilumab 300 mg Q1W ($n = 319$; not included in pooled data), or placebo ($n = 315$); in CAFÉ, all patients received TCS and were randomized to dupilumab 300 mg Q2W ($n = 107$), dupilumab 300 mg Q1W ($n = 110$; not included in pooled data), or placebo ($n = 108$)

^cWeighted median values

^dFor the baricitinib trials, Itch NRS is reported, and for the dupilumab studies, peak pruritus is reported. The phase 2b trial reported both itch and pruritus NRS

^ePlacebo only

Table 3 Results of the indirect treatment comparison of baricitinib and dupilumab in adult patients with moderate-to-severe atopic dermatitis (AD)

Outcome	Therapy (population)	BARI 2 mg versus DUPI 300 mg Q2W	BARI 4 mg versus DUPI 300 mg Q2W
Relative risk (95% CI)			
EASI75 at Week 4	Monotherapy (pop. A)	1.32 (0.66, 2.63), $p = 0.427$	1.84 (0.96, 3.52), $p = 0.064$
	TCS combo therapy (pop. A)	1.00 (0.49, 2.02), $p = 0.990$	1.45 (0.74, 2.85), $p = 0.281$
	TCS combo therapy (pop. B)	1.35 (0.49, 3.69), $p = 0.559$	2.19 (0.80, 5.99), $p = 0.128$
EASI75 at week 16	Monotherapy (pop. A)	0.66 (0.41, 1.05), $p = 0.081$	0.82 (0.52, 1.30), $p = 0.404$
	TCS combo therapy (pop. A)	0.62 (0.38, 1.02), $p = 0.058$	0.69 (0.43, 1.11), $p = 0.129$
	TCS combo therapy (pop. B)	0.76 (0.42, 1.38), $p = 0.365$	0.87 (0.46, 1.63), $p = 0.656$
Itch NRS \geq 4 point improvement at week 4	Monotherapy (pop. A)	1.49 (0.66, 3.33), $p = 0.337$	2.62 (1.22, 5.61), $p = 0.013$
	TCS combo therapy (pop. A)	1.14 (0.69, 2.91), $p = 0.345$	2.16 (1.08, 4.31), $p = 0.029$
	TCS combo therapy (pop. B)	1.76 (0.55, 5.66), $p = 0.341$	2.98 (0.93, 9.59), $p = 0.066$
Itch NRS \geq 4 point improvement at week 16	Monotherapy (pop. A)	0.65 (0.36, 1.17), $p = 0.147$	0.95 (0.55, 1.65), $p = 0.866$
	TCS combo therapy (pop. A)	0.63 (0.37, 1.08), $p = 0.096$	0.73 (0.43, 1.23), $p = 0.240$
	TCS combo therapy (pop. B)	0.87 (0.34, 2.22), $p = 0.768$	1.45 (0.56, 3.71), $p = 0.442$
Mean difference in change from baseline (95% CI)			
CFB DLQI at week 4	Monotherapy (pop. A)	1.79 (0.33, 3.25), $p = 0.016$	-0.11 (-1.34, 1.12), $p = 0.86$
	TCS combo therapy (pop. A)	1.07 (-0.78, 2.92), $p = 0.256$	-0.62 (-2.46, 1.22), $p = 0.509$
	TCS combo therapy (pop. B)	0.56 (-1.45, 2.57), $p = 0.585$	-0.95 (-3.11, 1.21), $p = 0.388$

Table 3 continued

Outcome	Therapy (population)	BARI 2 mg versus DUPI 300 mg Q2W	BARI 4 mg versus DUPI 300 mg Q2W
CFB DLQI at week 16	Monotherapy (pop. A)	2.05 (0.53, 3.56), $p = 0.008$	0.68 (−0.77, 2.14), $p = 0.358$
	TCS combo therapy (pop. A)	2.48 (0.46, 4.50), $p = 0.016$	1.09 (−0.93, 3.11), $p = 0.291$
	TCS combo therapy (pop. B)	3.38 (1.18, 5.58), $p = 0.003$	2.00 (−0.41, 4.41), $p = 0.104$

For EASI75 and Itch NRS ≥ 4 , relative risk < 1 indicates a result favoring dupilumab. Relative risk > 1 indicates a result favoring baricitinib. For DLQI, MDcfc > 0 indicates a result favoring dupilumab and MDcfc < 0 favors baricitinib. Results that attained statistical significance are given in bold text

BARI baricitinib, *DLQI* Dermatology Life Quality Index, *DUPI* dupilumab, *EASI* Eczema Area and Severity Index, *NRS* Numeric Rating Scale, *Q_xW* every x weeks

statistically significant differences were evident, although RR values numerically favored dupilumab except for baricitinib 4 mg in population B. At week 4, however, ≥ 4 -point itch NRS improvement was significantly more likely to be seen with baricitinib 4 mg than dupilumab in population A for both monotherapy and TCS combination trials. In population B, there were no statistically significant differences between baricitinib 2 or 4 mg compared with dupilumab in achieving ≥ 4 -point itch improvement at week 16; RR values numerically favored dupilumab for these comparisons apart from the ≥ 4 -point itch improvement seen in baricitinib 4 mg.

For DLQI, no significant differences were observed in MDcfc between baricitinib 4 mg and dupilumab as monotherapy or TCS combination therapy in either population at week 4 or week 16. However, DLQI at week 4 significantly favored dupilumab over baricitinib 2 mg in the population A monotherapy group. At week 16, DLQI MDcfc significantly favored dupilumab versus baricitinib 2 mg as both monotherapy in population A and TCS combination therapy in population A. This difference was also seen in population B at week 16 in our analysis. While these differences were statistically significant, they did not meet the criteria for being

clinically meaningful, where a meaningful clinical difference has been determined to be 4 [13].

DISCUSSION

This indirect comparison analysis found that baricitinib and dupilumab might have similar efficacy across EASI75, ≥ 4 -point improvement in itch NRS, and DLQI improvement (baricitinib 4 mg) after 16 weeks of treatment, confirming the findings of a recently published network meta-analysis (NMA) and extending them to an earlier time point (week 4) [14].

For earlier time points, baricitinib 4 mg was associated with a higher likelihood of an improvement in itch relative to dupilumab. This finding is largely in keeping with the existing evidence on baricitinib and other JAK 1/2 inhibitors, where improvements in itch have been observed as early as one day after treatment initiation [15, 16]. When asked, patients often rate itch as the symptom they find most bothersome and rate as their most important treatment goal [17, 18]. The increased expression of pruritogens, including TSLP, IL-4, IL-13, and IL-31, is thought to be most important for itch induction in AD [19, 20]. These pruritogens may signal via JAKs

[21] and consequently be directly inhibited by baricitinib. Such inhibition may explain baricitinib's ability to rapidly reduce itch. By week 16, itch improvement was comparable to that achieved by dupilumab. Our findings will serve to support clinical decision-making with regards to treatment options, not only several months into patients' therapy but also in the early weeks after treatment initiation.

H2H trial data, considered to be the highest form of evidence, can take time to emerge, perhaps delaying access to potentially beneficial therapies for health systems and patients. In such circumstances, NMA and ITCs like our study can help to provide valuable evidence before H2H data are available. In this case, we chose an ITC framework as only one other drug was identified by the SLR. Several factors should be considered when interpreting our results. Evidence identified by the systematic review was more limited for the TCS combination groups than for monotherapy. Also, it is possible that differences in trial design, such as TCS use not being standardized across trials and different washout periods, limit cross-trial comparability in the AD research landscape. Heterogeneity across trials designs and statistical analysis that impact study outcomes in AD clinical research has been identified as a challenge for healthcare providers [22], though in this instance, there is evidence that these may favor dupilumab [23]. The lack of longer-term follow-up in our analysis also represents a limitation. This was a function of the period of PBO-controlled observation within the trials themselves; comparisons can only be made where there are PBO data available to populate the models. This could be resolved by the conduct of full H2H trials with a longer follow-up period, but such analysis lies outside the scope of this work. We did not assess differences in safety outcomes between the competing treatments.

CONCLUSIONS

Baricitinib represents an approved oral treatment option for adult patients with moderate-to-severe AD that potentially offers more rapid

improvement in itch, a key symptom for patients, while it might also provide similar efficacy in terms of EASI75 and DLQI outcomes compared with dupilumab based on indirect evidence [24–28].

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. Data sharing is not applicable to this article as no new datasets were generated or analyzed during the current study.

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