JAK inhibitors and monoclonal antibodies for the treatment of atopic dermatitis: effectiveness and value

A summary from the Institute for Clinical and Economic Review's New England Comparative Effectiveness Public Advisory Council

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Atopic dermatitis is a chronic and relapsing inflammatory skin condition characterized by itching and dry skin. It frequently begins during childhood and persists into adulthood in about half of affected children.[1] In the United States, atopic dermatitis is estimated to affect about 11%–15% of children and 7%–10% of adults.[2-5] Although the symptoms of atopic dermatitis vary in their severity, severe itching often disrupts sleep, leading to daytime tiredness, psychological stress, and impaired performance at school and work.[6-8] Furthermore, the aesthetic effect of chronic atopic dermatitis can lead to social stress and isolation. The overall US costs associated with atopic dermatitis are estimated to be $5.3 billion, including over $1 billion in health care costs.[9,10]

Disease severity is difficult to characterize because it depends on the amount and location of skin involved, its appearance, and the subjective effect of symptoms. However, epidemiologic studies have reported that most children with atopic dermatitis have mild disease, with approximately 12%–26% having moderate disease and 4%–7% having severe disease.[1,11,12] There is less evidence on the severity of disease in adults; however, the moderate to severe form of the disease appears to be more common in adults.[13]

Treatment strategies for atopic dermatitis include hydration with moisturizers and emollients, short-term intermittent treatment with topical corticosteroids, and long-term maintenance with topical calcineurin inhibitors or crisaborole.[14] For those with atopic dermatitis not controlled with topical therapies, phototherapy or general systemic immunomodulators, such as cyclosporine and azathioprine, are used.[15] In addition, dupilumab, an IL-4 receptor antagonist that became available in the United States in 2017 as the first approved biologic treatment for atopic dermatitis, is now a commonly used systemic immunomodulator for moderate to severe disease.[16]

There are several emerging treatments that are expected to play important roles in therapy. Tralokinumab is an IL-13 receptor antagonist currently under US Food and Drug Administration (FDA) review for patients with moderate to severe atopic dermatitis. Similar to dupilumab, tralokinumab is given subcutaneously. In addition, ruxolitinib cream, a topical janus kinase (JAK) inhibitor, was recently approved by the FDA for patients with mild to moderate atopic dermatitis. Oral JAK inhibitors abrocitinib, baricitinib, and upadacitinib are also being evaluated for patients with moderate to severe atopic dermatitis, but the FDA has extended the review period for these drugs because of recent data that

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TABLE 1 Proportions of Patients Achieving EASI Thresholds as Estimated From Bayesian Network Meta-Analysis

Treatment	EASI 50 (95% CrI)[a]	EASI 75 (95% CrI)[b]	EASI 90 (95% CrI)[c]
Placebo	0.21 (0.20-0.23)	0.12 (0.1-0.13)	0.05 (0.04-0.06)
Dupilumab 300 mg Q2W	0.64 (0.58-0.70)	0.49 (0.42-0.55)	0.32 (0.27-0.38)
Abrocitinib 100 mg	0.55 (0.45-0.65)	0.40 (0.30-0.50)	0.24 (0.17-0.33)
Abrocitinib 200 mg	0.73 (0.64-0.81)	0.58 (0.49-0.68)	0.41 (0.32-0.52)
Baricitinib 1 mg	0.31 (0.25-0.39)	0.19 (0.14-0.25)	0.09 (0.07-0.14)
Baricitinib 2 mg	0.44 (0.36-0.52)	0.29 (0.23-0.37)	0.16 (0.12-0.22)
Tralokinumab 300 mg	0.46 (0.38-0.53)	0.31 (0.24-0.38)	0.17 (0.13-0.23)
Upadacitinib 15 mg	0.70 (0.64-0.76)	0.55 (0.48-0.61)	0.38 (0.31-0.45)
Upadacitinib 30 mg	0.80 (0.75-0.84)	0.67 (0.61-0.73)	0.50 (0.44-0.57)

[a]*EASI 50: a percentage improvement of EASI score from baseline that is ≥50%.*
[b]*EASI 75: a percentage improvement of EASI score from baseline that is ≥75%.*
[c]*EASI 90: a percentage improvement of EASI score from baseline that is ≥90%.*
CrI = credible interval; EASI = Eczema Area Severity Index; Q2W = once every 2 weeks.

have raised questions about the safety of oral JAK inhibitors approved for other conditions.[17]

The Institute for Clinical and Economic Review (ICER) evaluated tralokinumab, abrocitinib, baricitinib, upadacitinib, and ruxolitinib cream for atopic dermatitis. This report presents the summary of our systematic literature review and cost-effectiveness analysis and highlights the key policy recommendations discussed at the New England Comparative Effectiveness Public Advisory Council's public meeting on July 23, 2021. The detailed report is available at https://icer.org/wp-content/uploads/2020/12/Atopic-Dermatitis_Final-Evidence-Report_081721.pdf.

Summary of Findings

We evaluated the clinical effectiveness of tralokinumab and the 3 oral JAK inhibitors (abrocitinib, baricitinib, and upadacitinib) vs placebo and vs dupilumab in patients with moderate to severe atopic dermatitis. In addition, we examined the clinical effectiveness of ruxolitinib cream in patients with mild to moderate atopic dermatitis.

For the moderate to severe population, 3 randomized controlled trials (RCTs) of tralokinumab,[18,19] 5 RCTs of abrocitinib,[20-22] 5 RCTs of baricitinib,[23-29] 5 RCTs of upadacitinib,[30-32] and 6 RCTs of dupilumab met our inclusion criteria.[33-35] The RCTs were predominantly placebo controlled, with only 2 head-to-head trials (abrocitinib vs dupilumab and updacitinib vs dupilumab). Of these trials, 14 were monotherapy trials, and 6 were combination trials that permitted use of background topical medication. The majority of trials for the 4 new therapies enrolled patients aged at least 18 years, except for abrocitinib and upadacitinib trials, which enrolled patients aged at least 12 years.

Abrocitinib, baricitinib, tralokinumab, and upadacitinib all improved skin outcomes compared with placebo, and, where assessed, appeared to improve itch, sleep, and quality of life for patients with moderate to severe atopic dermatitis. The few adolescent patients included in the trials of abrocitinib and upadacitinib appeared to have similar outcomes compared with adults.

Using a Bayesian network meta-analysis (NMA), we combined outcome data from all eligible monotherapy RCTs to indirectly compare the interventions to each other. Similar to what was observed in the head-to-head trials, the NMA suggests that the higher doses of abrocitinib and upadacitinib were similar or better than dupilumab. For example, compared with dupilumab, relative risks (RR) for achieving at least a 75% reduction in the Eczema Area and Severity Index (EASI 75) were 1.20 (95% credible interval [CrI] = 0.97-1.46) and 1.38 (95% CrI = 1.23-1.56) for abrocitinib 200 mg and updacitinib 30 mg, respectively. In contrast, dupilumab was significantly better than tralokinumab (RR = 1.58; 95% CrI = 1.25-2.03) and both doses of baricitinib (higher dose, RR = 1.64; 95% CrI = 1.28-2.15) on EASI 75 (and other main outcomes); however, there is substantial uncertainty in these comparisons because of the lack of head-to-head evidence. Based on the NMA, the expected proportion of patients who achieved different EASI thresholds is presented in Table 1.

Most adverse events (AEs) observed in the trials were of mild to moderate severity. The most commonly reported AEs with greater incidence than placebo were nausea, conjunctivitis, and herpetic infection. The incidence of discontinuation due to AEs and serious AEs were low and generally similar among these agents. However, evidence from trials evaluating JAK inhibitors at longer time points for other indications suggests an increased risk of serious AEs, such as reactivation of herpes zoster, malignancy, thromboembolic events, and cardiovascular events[36]; this has led the FDA to place black box warnings

TABLE 2 Health Care Perspective

Treatment	Comparator	Incremental cost-effectiveness ratios	
		Cost per QALY[b]	Cost per evLYG[b]
Abrocitinib[a]	Standard of care	$148,300	$148,300
Baricitinib		$71,600	$71,600
Tralokinumab[a]		$129,400	$129,400
Upadacitinib		$248,400	$248,400
Dupilumab		$110,300	$110,300
Abrocitinib[a]	Dupilumab	$303,400	$303,400
Baricitinib		Less costly, less effective	Less costly, less effective
Tralokinumab[a]		Less costly, less effective	Less costly, less effective
Upadacitinib		$1,912,200	$1,912,200

[a]*Using placeholder price.*
[b]*The cost per QALY and cost per evLYG ratios were the same, given that the treatments have not been shown to lengthen life.*
evLYG = equal value life-year gained; QALY = quality-adjusted life-year.

on this class of agents and has delayed the approval of these agents for atopic dermatitis.

In the mild to moderate population, topical ruxolitinib cream was significantly better than vehicle cream (placebo) on all skin and patient-reported outcomes in 2 RCTs. Even though ruxolitinib cream also appeared to be more effective than a medium potency topical corticosteroid, it was not compared with more potent topical corticosteroids, and differences in trial designs precluded indirect quantitative comparisons across topical therapies. The most commonly reported AEs included application site burning and pruritus, and the incidence of these AEs was lower in the ruxolitinib cream arms than placebo arm. As a topical JAK inhibitor therapy, safety concerns are likely not as great as with oral JAK inhibitors; however, its FDA approval came with the same black box warnings seen for other JAK inhibitors, highlighting the risk of serious infections malignancies and serious cardiovascular-related events.

LIMITATIONS OF THE CLINICAL EVIDENCE

Tralokinumab and JAK inhibitors are therapies with novel mechanisms of action affecting the body's immune system, and we lack long-term safety data for patients with atopic dermatitis. In addition, due to the limited head-to-head data on these agents, we used indirect analyses to compare abrocitinib, baricitinib, tralokinumab, and upadacitinib with each other and to dupilumab. However, the results of indirect analyses are more uncertain than when the therapies are compared directly. Finally, there is limited information available about the relative benefits and harms of these new therapies in important subgroups, particularly among adolescents aged 12-17 years and African-Americans, given the significant effect of atopic dermatitis in these subgroups.

LONG-TERM COST-EFFECTIVENESS

We evaluated the cost-effectiveness of abrocitinib, baricitinib, tralokinumab, and upadacitinib vs standard of care and vs dupilumab in adult patients with moderate to severe atopic dermatitis from a US health care sector perspective using an adapted Markov model previously developed for dupilumab.[37] We did not evaluate the cost-effectiveness of ruxolitinib cream.

The Markov model was developed with health states based on treatment response measured by EASI scores.[38] Health states were categorized by the percent decrease in EASI score from baseline after a patient begins an intervention: less than 50% decrease (no response), 50%-74% decrease (EASI 50), 75%-89% decrease (EASI 75), and 90%-99% decrease (EASI 90). Costs and outcomes were discounted at an annual rate of 3% over a 5-year time horizon.

The model was informed by the results of the ICER NMA previously described, before relevant economic models, other published studies on atopic dermatitis, and stakeholder input, including manufacturer-submitted data.[37,39] At the time of the report, there were no available prices for abrocitinib and tralokinumab, so we used placeholder prices to generate cost-effectiveness results. For abrocitinib, we used the average of the net prices of baricitinib and upadacitinib. For tralokinumab, the net price of dupilumab was used as the placeholder price. Full details on ICER's cost-effectiveness analysis and model are available on ICER's website at https://icer.org/wp-content/uploads/2020/12/Atopic-Dermatitis_Final-Evidence-Report_081721.pdf.

Results from our analysis showed that when compared with standard of care, the incremental cost-effectiveness ratio was lowest for baricitinib at $71,600 per quality-adjusted life-year (QALY) and highest for upadacitinib at $248,400 per QALY. QALY results are identical to those using equal value of life-years gained (evLYG), given that these treatments are not expected to extend life. Compared with dupilumab, model results showed that

TABLE 3 Votes on Other Contextual Considerations

Contextual consideration	Very low priority	Low priority	Average priority	High priority	Very high priority
Acuity of need for treatment of individual patients based on the severity of the condition being treated	0	0	6	6	1
Magnitude of the lifetime impact on individual patients of the condition being treated	0	0	3	9	1

TABLE 4 Votes on Other Benefits or Disadvantages

Potential other benefit or disadvantage	Major negative effect	Minor negative effect	No difference	Minor positive effect	Major positive effect
Patients' ability to achieve major life goals related to education, work, or family life	0	0	0	4	9
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life	0	0	0	6	7
Society's goal of reducing health inequities	0	1	7	4	1
What are the relative effects of the JAK inhibitors as a class vs dupilumab on patients' ability to manage and sustain treatment given the complexities of the regimens?	0	0	4	8	1
What are the relative effects of tralokinumab vs dupilumab on patients' ability to manage and sustain treatment given the complexities of the regimens?	0	0	8	5	0

baricitinib and tralokinumab were both less costly and less effective. Abrocitinib and upadacitinib had incremental cost-effectiveness ratios of approximately $300,000 and $1.9 million per QALY, respectively. Detailed results are presented in Table 2.

To achieve a cost per QALY threshold of $100,000-$150,000 relative to standard of care, the annual price of the assessed treatments would need to fall within the following ranges: $30,600-$41,800 for abrocitinib; $24,400-$33,300 for baricitinb; $25,700-$35,000 for tralokinumab; $30,400-$41,500 for upadacitinib; and $29,000-$39,500 for dupilumab.

LIMITATIONS OF THE COST-EFFECTIVENESS MODEL

The clinical trial efficacy was extrapolated beyond the length of the trials, which assumes continued effectiveness and adherence to treatment. Additionally, the model assumes that levels of EASI response are the primary driver of differences in health-related quality of life; however, the treatments may have differential effects on itch and sleep that vary in their correlation with EASI response scores. There may also be incremental effects of these treatments on quality of life in subpopulations of people with atopic dermatitis and co-occurring asthma or chronic rhinosinusitis, which are not explicitly captured in the model. Finally, NMA analyses informed the efficacy estimates in the model, and as noted earlier, indirect analyses are more uncertain than when the therapies are compared directly.

Policy Discussion

The New England Comparative Effectiveness Public Advisory Council (CEPAC) convened on July 23, 2021, to publicly deliberate on the clinical and cost-effectiveness of treatments of atopic dermatitis. The New England CEPAC is an independent appraisal committee composed of medical evidence experts, including practicing clinicians, methodologists, and leaders in patient engagement and advocacy. Their deliberation included input from clinical experts and patient representatives with atopic dermatitis expertise and formal comments from manufacturers and the public.

Following the discussion, the CEPAC members deliberated on key questions raised by ICER's report. Based on the evidence in the clinical trials and ongoing concerns

about long-term safety with oral JAK inhibitors, the panel votes were split as to the net health benefit of adding abrocitinib (8-5), baricitinib (7-6), and upadacitinib (9-4) to usual care compared with usual care alone. The panel voted 11-2 that the clinical evidence was adequate to demonstrate a greater net health benefit for tralokinumab plus usual care compared with usual care alone. Finally, the panel voted 12-1 that the clinical evidence was adequate to demonstrate a greater net health benefit for ruxolitinib cream plus usual care compared with usual care alone in mild to moderate atopic dermatitis.

The CEPAC panel also voted on "other potential benefits" and "contextual considerations" as part of a process intended to signal to policymakers whether there are important considerations when making judgments about long-term value for money not adequately captured in analyses of clinical and/or cost-effectiveness. The results of these votes are shown in Tables 3 and 4.

The culminating vote of the CEPAC panel, intended to reflect its integration of the relevant elements of the value assessment framework, was on the "long-term value for money." The panelists did not vote on abrocitinib and tralokinumab because prices were not available for these drugs at the time of the public meeting. However, baricitinib and upadacitinib have a known price, since they are approved for other indications. For baricitinib, the panel members voted that its long-term value for money is intermediate (7/13 votes) or high (6/13 votes) compared with usual care. The majority of the panel voted that upadacitinib represents a low value for money at the current price compared with usual care (10/13 votes).

The meeting concluded with a policy roundtable where representatives from insurers and manufacturers joined clinical experts and patient representatives and discussed how best to apply the evidence and additional considerations into clinical practice and pricing and insurance coverage policies. The full set of policy recommendations can be found in the Final Evidence Report on the ICER website. The key policy recommendations are as follows:

Recommendation: All stakeholders have a responsibility and an important role in ensuring that effective new treatment options for patients with atopic dermatitis are introduced in a way that will help reduce health inequities.

Recommendation: Some considerations for prior authorizations:

Patient eligibility: Age criteria are likely to follow the FDA label, so payers should have efficient mechanisms for clinicians to seek coverage exceptions for patients with serious unmet needs near the cutoff for the age necessary for coverage.

Clinical eligibility: Given the lack of clear consensus on how "moderate to severe" atopic dermatitis is defined, payers should operationalize the definition/measure of disease severity so that it is kept broad, is inclusive of multiple measures of disease intensity, and is clinically relevant for clinicians.

Duration of coverage and renewal criteria: Payers should establish an initial coverage period of 6-12 months, which is long enough for dose titration, assessment of side effects, or disease progression.

Recommendation: Payers should only use step therapy when it provides adequate flexibility to meet the needs of diverse patients and when the implementation can meet high standards of transparency and efficiency. For example, payers establishing step therapy with less expensive systemic agents and/or phototherapy should allow patients and clinicians to choose from multiple options rather than require patients to try all options.

Recommendation: If multiple agents for severe atopic dermatitis are approved, payers should make available at least 1 biologic (dupilumab and/or tralokinumab) and at least 1 JAK inhibitor, given how different these classes are in their onset of action and their risk profile.

Recommendation: Manufacturers should establish long-term registries that can be used to assess the benefits and harms of chronic use of oral JAK inhibitors for patients with atopic dermatitis. There are potentially serious risks and adverse events associated with JAK inhibitors, so long-term follow-up is warranted.

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