


Efficacy and Safety of Dupilumab in Adolescents with Uncontrolled Atopic Dermatitis: Systematic Review

Kenny Andrianus, Triana Agustin, Windy Atika Hapsari
KSM Dermatologi dan Venereologi, Fakultas Kedokteran Universitas Indonesia/
RSUP Nasional Dr. Cipto Mangunkusumo Jakarta, Indonesia

ABSTRACT

Introduction: Up to 24.6% of young adults worldwide suffer from atopic dermatitis. Dupilumab was originally intended for adults with uncontrolled moderate to severe atopic dermatitis. As of March 2019, it has been approved by the US Food and Drug Administration (FDA) for use in adolescents aged 12 to 17. This article aims to evaluate the efficacy and safety of dupilumab in adolescents with uncontrolled moderate to severe atopic dermatitis compared to standard therapy. **Methods:** A literature search was conducted in June 2020 across Cochrane, EBSCO, and PubMed using specific medical subject heading (MeSH) terms. Inclusion and exclusion criteria were applied. Only relevant articles were selected and appraised using the Center for Evidence-based Medicine (CEBM) tools. **Results:** Two articles were selected: 1 RCT and 1 cohort study, with 251 and 40 subjects, respectively. Both studies showed statistically significant reductions across all parameters evaluated with Investigator Global Assessment (IGA), Eczema Area and Severity Index (EASI), and Pruritus Numerical Rating Scales. The effectiveness of dupilumab is positively correlated with dosage, frequency, and treatment duration. In both studies, the 4 mg per kg body weight group compared to the 2 mg per kg body weight group, and the every 2 weeks' protocol compared to the every 4 weeks' protocol showed better effectiveness. The most common side effects include conjunctivitis, skin infections, and local reactions due to injections. **Conclusion:** Dupilumab is effective for treating uncontrolled atopic dermatitis in adolescents. The IGA, EASI, and pruritus NRS parameters showed significant reductions. Side effects associated with dupilumab are minimal and well-tolerated.

Keywords: Adolescents, dupilumab, efficacy and safety, uncontrolled atopic dermatitis.

ABSTRAK

Pendahuluan: Sekitar 24,6% orang dewasa muda di seluruh dunia menderita dermatitis atopik. *Dupilumab* pada awalnya ditujukan untuk orang dewasa dengan dermatitis atopik derajat sedang hingga berat yang tidak terkontrol. Pada Maret 2019, Food and Drug Administration (FDA) AS telah menyetujui *dupilumab* untuk digunakan pada remaja berusia 12 hingga 17 tahun. Artikel ini mengevaluasi keamanan dan efektivitas *dupilumab* pada remaja dengan dermatitis atopik derajat sedang hingga berat yang tidak terkontrol dibandingkan dengan terapi standar. **Metode:** Pencarian literatur pada bulan Juni 2020 pada Cochrane, EBSCO, dan PubMed menggunakan istilah subjek medis khusus (MeSH). Kriteria inklusi dan eksklusi ditetapkan. Hanya artikel yang relevan yang dipilih dan ditelaah menggunakan kriteria Center for Evidence-based Medicine (CEBM). **Hasil:** Dua artikel dipilih: 1 uji acak terkontrol dan 1 studi kohort, dengan masing-masing 251 dan 40 subjek. Kedua studi menunjukkan pengurangan yang statistik signifikan pada semua parameter evaluasi menggunakan skor *Investigator Global Assessment* (IGA), *Eczema Area and Severity Index* (EASI), dan *Pruritus Numerical Rating Scale*. Efektivitas *dupilumab* berkorelasi positif terhadap dosis, frekuensi, dan durasi pengobatan. Pada kedua penelitian, efektivitas lebih baik pada kelompok 4 mg per kgBB dibandingkan kelompok 2 mg per kgBB serta kelompok pemberian setiap 2 minggu dibandingkan setiap 4 minggu. Efek samping tersering antara lain konjungtivitis, infeksi kulit, dan reaksi lokal akibat suntikan. **Simpulan:** *Dupilumab* efektif mengobati dermatitis atopik tidak terkontrol pada populasi remaja. Parameter IGA, EASI, dan pruritus NRS turun signifikan. Efek samping terkait penggunaan *dupilumab* minimal dan dapat ditoleransi dengan baik. **Kenny Andrianus, Triana Agustin, Windy Atika Hapsari. Efikasi dan Keamanan *Dupilumab* pada Remaja dengan Dermatitis Atopik Tidak Terkontrol: Tinjauan Sistematis.**

Kata Kunci: Remaja, *dupilumab*, efikasi dan keamanan, dermatitis atopik tidak terkontrol.

https://doi.org/10.55175/cdk.v53i07.2072

**The original article is in Bahasa Indonesia, translated into English by the editorial board and consented to by all authors*

Alamat Korespondensi *kenny.andrianus@gmail.com*

PENDAHULUAN

Atopic dermatitis (AD) is a chronic inflammatory skin disease commonly found in children. Among young adults worldwide, 24.6% have AD. The clinical manifestations of moderate-to-severe AD include extensive eczematous lesions accompanied by xerosis and intense itching. Some patients do not experience significant improvement with oral and topical therapy.[1–3]

Dupilumab is a biologic agent for the management of uncontrolled moderate-to-severe atopic dermatitis. Dupilumab is a monoclonal antibody that specifically binds the alpha subunit of IL-4, thereby inhibiting the release of IL-4 and IL-13. These cytokines initiate a T helper 2 (Th2) immune response, which is the primary cause of allergic reactions in patients with atopic dermatitis.[4–6] In March 2019, this drug was approved by the U.S. Food and Drug Administration (FDA) for the treatment of atopic dermatitis in adolescents aged 12 to 17 years.[2,3,7]

This medication is administered subcutaneously and is available in 200 mg and 300 mg doses. The initial dose ranges from 400 to 600 mg, and a maintenance dose of 300 mg is administered every 2 to 4 weeks. The duration of treatment varies from 3 to 12 months, depending on the severity.[8–10] This article was written to evaluate the efficacy and safety of dupilumab in adolescents with moderate-to-severe uncontrolled AD.

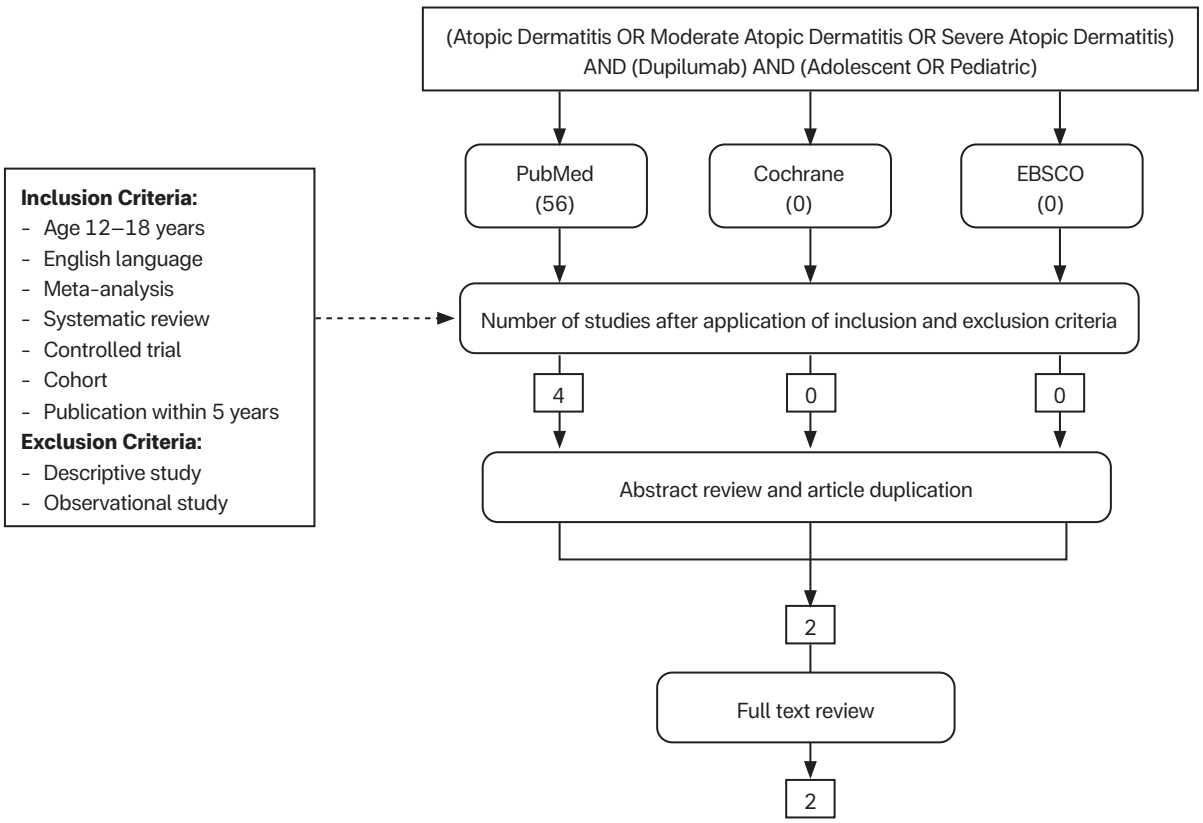
METHODS

A literature search was conducted in June 2020 via Cochrane, EBSCO, and PubMed using specific Medical Subject Headings (MeSH) terms. The search used the terms "atopic dermatitis," "moderate atopic dermatitis," "adolescents," "severe atopic dermatitis," "dupilumab," and "corticosteroids." Only reports meeting the inclusion criteria-cohort studies, randomized controlled trials, systematic reviews, meta-analyses, moderate or severe atopic dermatitis, adolescents, and internationally recognized English-language papers and articles published within the past 5 years-were included in this review. Exclusion criteria included populations under 12 or over 18 years of age, mild atopic dermatitis, observational studies, and articles older than 5 years. Articles were screened and selected independently to minimize selection bias. Only relevant articles were selected and assessed using a questionnaire from the Center for Evidence-based Medicine (CEBM). The literature search process is outlined in the **Scheme**.

RESULTS

Two articles were selected: 1 randomized controlled trial and 1 cohort study, with 251 and 40 subjects, respectively. Both articles were rated as being of good quality based on the assessment form. Disease progression was evaluated using the Investigator's Global Assessment (IGA) score, the Eczema Area and Severity Index (EASI), and the Pruritus Numerical Rating Scale (NRS). The main strength of this review is its specific focus on adolescents (12–17 years), whereas many previous reviews included mixed pediatric and adult populations. In addition, only studies with a higher level of evidence (one randomized controlled trial and one prospective cohort study) were included.

The first study by Cork, *et al*., was a phase II study involving 40 subjects divided into two intervention groups based on initial dupilumab doses of 2 mg vs. 4 mg/kg body weight,



Scheme. Literature search results.

followed for 52 weeks. Both groups began showing a statistically significant reduction in EASI scores ($p < 0.05$) at weeks 12 and 52. The first group (2 mg/kg) experienced a 34% reduction in EASI scores, and the second group (4 mg/kg) a 51% reduction at week 12. By week 52, the results were even more significant, with an 85% and 84% reduction in EASI scores in the two groups, respectively ($p < 0.05$).[3] Efficacy was assessed using IGA scores and pruritus scores, showing a statistically significant reduction ($p < 0.05$). The proportions of patients with IGA 0 and 1 in the 2 mg vs. 4 mg/kg body weight groups were 10% vs. 35% at week 12 and 38% vs. 44% at week 52. Additionally, there was a 40% reduction in pruritus (NRS) scores ≥ 4 points for both groups at week 12 and 72% at week 52. Improvements of ≥ 3 points were observed in 50% of patients at week 12 and 78% at the end of the study.[3]

The second study by Simpson, *et al*., was a double-blind, randomized controlled trial involving 251 subjects divided into 3 groups. Patients in the intervention group received 200 or 300 mg of dupilumab every 2 or 4 weeks, and the placebo group received a placebo for 16 weeks. Patients weighing less than 60 kg received 200 mg, while those weighing more than 60 kg received 300 mg. In this study, EASI, IGA, and NRS scores decreased significantly ($p < 0.001$). The proportion of subjects achieving EASI-75 in the first, second, and placebo groups was 41.5%, 38.1%, and 8.2%, respectively ($p < 0.001$). By week 16, 24.4% of patients in the 2-week interval group and 17.9% in the 4-week interval group achieved an IGA score of 0 or 1, compared to 2.4% in the placebo group. Improvement in pruritus NRS score of ≥4 points was 47.9% in the every-2-week group, 45.5% in the every-4-week group, and 19.0% in the placebo group[7] (**Table 1**).

The most common side effects associated with dupilumab include conjunctivitis, skin infections, and local reactions at the injection site. The incidence rates of conjunctivitis in the study by Cork, *et al*., at doses of 2 mg and 4 mg were 18% and 16%, respectively; the incidence rates of skin infections were 18% and 11%, respectively; and the incidence rates of local reactions was 29% and 42%, respectively. In the study by Simpson, *et al*., a comparison of side effects between groups with dosing intervals of every 2 weeks, 4 weeks, and placebo showed, among others, conjunctivitis at 10.8%, 9.8%, and 4.7%, skin infections at 13.3% and 20.0%, and local reactions at 6.0%, 8.5%, and 3.5%.

Dupilumab has a favorable safety and tolerability profile compared to other systemic agents, making it the first-line choice for long-term therapy in adolescents with moderate-to-severe atopic dermatitis. Serious systemic side effects are rarely reported, and most patients can continue therapy without significant disruption.[10–12] The efficacy of dupilumab has also been shown to be superior in meta-analysis studies compared to methotrexate and cyclosporine, particularly regarding clinical success and low rates of treatment discontinuation due to adverse effects.[12] In addition to clinical improvement, dupilumab improves quality of life, including sleep and social functioning.[13] Dupilumab is now recognized as part of the standard of care for severe atopic dermatitis unresponsive to conventional therapy, in both adolescents and adults.[11,14]

DISCUSSION

Both studies showed a reduction in scores across all assessment parameters. Most subjects had extensive atopic dermatitis, and most were not well-controlled with corticosteroids or other immunosuppressants (cyclosporine or azathioprine).[3,7]

The studies by Cork, *et al*.,[3] and Simpson, *et al*.,[7] showed significant improvement in all three parameters (IGA, EASI, and Pruritus NRS). The degree of score reduction was greater with higher doses, more frequent administration, and longer therapy duration. The EASI score in the 4 mg/kg group decreased more significantly compared to the 2 mg/kg group (week 12). By week 52, both groups achieved reductions in EASI scores of up to 85%. The proportion of subjects achieving IGA score of 0 or 1 by week 12 was higher in the 4 mg/kg body weight group than in the 2 mg/kg body weight group. By week 52, 40% of patients in both groups achieved a reduction in Pruritus NRS scores of ≥ 4 points.[3]

A similar trend was observed in the second study.[7] The every-2-week dupilumab group outperformed the every-4-week group. The proportion of patients achieving EASI-75 at week 16 was 41.5% (every 2 weeks) vs. 38.1% (every 4 weeks). The difference between the treatment and placebo groups was 33.2% (every 2 weeks) (95% CI, $p < 0.001$) vs. 29.9% (every 4 weeks) (95% CI, $p < 0.001$). IGA and NRS scores showed the same trend. Subjects with IGA scores of 0 and 1 were more numerous, and NRS pruritus scores

Table 1. Parameters of atopic dermatitis.

	Cork, *et al*.[3]	**Simpson, *et al*.**[7]
Number of patients	40	251
Dupilumab dosage	2 or 4 mg/kg body weight	300 mg (every 4 weeks) 200 mg/300 mg (every 2 weeks)
Reduction of EASI	(W12) 34% and 51% (W52) 85% and 84%	(W16) 47.5% and 51.6%
IGA 0–1 (%)	(W12) 10% and 35% (W52) 38% and 44%	(W16) 17.9% and 24.4%
Reduction in NRS pruritus score ≥ 4 (%)	(W12) 40% (W52) 72%	(W16) 26.5% and 36.6%

Abbreviations: EASI: Eczema area and severity index; IGA: Investigator's global assessment; NRS: Numerical rating scale.

Table 2. Side effects of dupilumab.

	Cork, *et al.*[3]	Simpson, *et al.*[7]
Dose	2 or 4 mg/kg body weight	300 mg (every 4 weeks) 200 mg/300 mg (every 2 weeks)
Reaction at the Injection Site	18% and 11%	6% and 8.5%
Conjunctivitis	18% and 16%	9% and 8%
Skin Infection	18% and 21%	1% and 2%

were higher in the group receiving treatment every 2 weeks compared to every 4 weeks ($p < 0.001$).[7] A comparison of adverse effects from both studies is presented in **Table 2**.

Both studies showed that a higher dose (2 mg vs. 4 mg/kg body weight), more frequent administration (every 2 weeks vs. every 4 weeks), and a longer duration of therapy (up to 52 weeks) resulted in better outcomes across all parameters.

The most common side effects of dupilumab are conjunctivitis, skin infections, and local reactions at the injection site. Conjunctivitis is associated with reduced goblet cell production due to IL-13 blockade.[9] According to studies,[3,4] the incidence of conjunctivitis and skin infections was higher at the 4 mg dose compared to the 2 mg dose. Similarly, the incidence of conjunctivitis and skin infections was higher with a dosing frequency of every 2 weeks compared to every 4 weeks. The incidence of local injection site reactions showed little correlation. The incidence of side effects appears to be slightly higher at higher doses. However, most were still well tolerated through the end of the study, and no subjects were discontinued.[11–13]

In addition to its favorable safety profile, dupilumab's primary advantage lies in its specific mechanism of action, which targets the IL-4 and IL-13 pathways, thereby suppressing the Th2 immune response without broadly compromising systemic immunity. This explains the low incidence of systemic infections and immunosuppressive effects typically observed with conventional systemic medications.[9,10] Recent consensus statements[8,14] also emphasize the importance of monitoring for ocular symptoms, particularly conjunctivitis, which is the most common side effect. However, most cases are mild and can be managed without discontinuing therapy.[10,15]

A meta-analysis by Drucker, *et al*., confirms that dupilumab has the best benefit-to-risk ratio, making it the primary treatment of choice for adolescents with atopic dermatitis refractory to corticosteroids or cyclosporine. Its effectiveness also includes improvement in patients' subjective symptoms, such as itching and sleep disturbances, which have a significant impact on adolescents' productivity and psychosocial well-being.[12,14]

CONCLUSION

Dupilumab is effective for the management of atopic dermatitis (AD) in adolescents, particularly for moderate-to-severe cases that are not controlled by conventional therapy. Based on evaluations of clinical parameters-the Eczema Area and Severity Index (EASI), Investigator Global Assessment (IGA), and Pruritus Numerical Rating Scale (NRS)-a statistically significant reduction in symptoms was observed across dose groups and treatment durations. The most commonly reported side effects were conjunctivitis, skin infections, and local injection site reactions; however, most were mild and well-tolerated without requiring treatment discontinuation. In addition to clinical improvement, dupilumab was associated with improved quality of life and reduced pruritus. Based on clinical evidence and the consensus of the latest treatment guidelines, dupilumab is considered a safe and effective biologic therapy for long-term use in adolescents with uncontrolled AD. Dupilumab should be considered as part of a systemic therapeutic approach for this patient population.

REFERENCES

1. Blauvelt A, de Bruin-Weller M, Gooderham M, Cather JC, Weisman J, Pariser D, et al. Long–term management of moderate–to–severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1–year, randomized, double–blinded, placebo–controlled, phase 3 trial. Lancet 2017;389(10086):2287–303. doi: 10.1016/S0140–6736(17)31191–1.
2. de Bruin-Weller M, Thaci D, Smith CH, Reich K, Cork MJ, Radin A, et al. Dupilumab with concomitant topical corticosteroid treatment in adults with atopic dermatitis with an inadequate response or intolerance to ciclosporin A: a randomized phase III trial (LIBERTY AD CAFE). Br J Dermatol. 2018;178(5):1083–101. doi: 10.1111/bjd.16156.
3. Cork MJ, Thaci D, Eichenfield LF, Arkwright PD, Hultsch T, Davis JD, et al. Dupilumab in adolescents with uncontrolled moderate–to–severe atopic dermatitis: results from a phase IIa open–label trial and subsequent phase III open–label extension. Br J Dermatol. 2020;182(1):85–96. doi:10.1111/bjd.18035
4. Paller AS, Jaworski JC, Simpson EL, Boguniewicz M, Russell JJ, Block JK, et al. Major comorbidities of atopic dermatitis: Beyond allergic disorders. Am J Clin Dermatol. 2018;19(6):821–38. doi: 10.1007/s40257-018-0383-4.

5. Tian J, Zhang D, Yang Y, Huang Y, Wang L, Yao X, et al. Global epidemiology of atopic dermatitis: a comprehensive systematic analysis and modelling. Br J Dermatol. 2023;190(1):55–61. doi: 10.1093/bjd/ljad339.
6. Sidbury R, Davis DM, Cohen DE, Cordoro KM, Berger TG, Bergman JN, et al. Guidelines of care for the management of atopic dermatitis: Section 3. Management and treatment with phototherapy and systemic agents. J Am Acad Dermatol. 2014;71(2):327–49. doi: 10.1016/j.jaad.2014.03.030.
7. Simpson EL, Paller AS, Siegfried EC, Boguniewicz M, Sher L, Gooderham MJ, et al. Efficacy and safety of dupilumab in adolescents with uncontrolled moderate to severe atopic dermatitis: a phase 3 randomized clinical trial. JAMA Dermatol. 2020;156(1):44–56. doi: 10.1001/jamadermatol.2019.3336.
8. Wollenberg A, Barbarot S, Bieber T, Christen-Zaech S, Deleuran M, Fink-Wagner A, et al. Consensus–based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I. J Eur Acad Dermatol Venereol. 2018;32(5):657–82. doi: 10.1111/jdv.14891.
9. Renert-Yuval Y, Guttman-Yassky E. New treatments for atopic dermatitis targeting beyond IL-4 and IL-13 cytokines. Ann Allergy Asthma Immunol. 2020 Jan;124(1):28–35. doi: 10.1016/j.anai.2019.10.005.
10. Gooderham MJ, Hong HCH, Eshtiaghi P, Papp KA. Dupilumab: a review of its use in the treatment of atopic dermatitis. J Am Acad Dermatol. 2018 Mar;78(3 Suppl 1):S28–S36. doi: 10.1016/j.jaad.2017.12.022.
11. Eichenfield LF, Flohr C, Sidbury R. Practical management of atopic dermatitis: current and emerging therapies. Pediatr Clin North Am. 2021;68(5):1037–52.
12. Drucker AM, Ellis AG, Jabbar-Lopez Z, Yiu ZZN, Arents BWM, Burton T, et al. Systemic immunomodulatory treatments for atopic dermatitis: protocol for a systematic review with network meta-analysis BMJ Open 2018;8:e023061. doi:10.1136/bmjopen-2018-023061.
13. Silverberg JI. Dupilumab treatment shows improvement in quality of life for atopic dermatitis patients. Cutis. 2019;103(4):218–20.
14. Wollenberg A, Christen–Zäch S, Taieb A, Paul C, Thyssen JP, de Bruin–Weller M, et al. European Task Force on Atopic Dermatitis: Position on dupilumab. J Eur Acad Dermatol Venereol. 2018;32(4):515–9. doi.org/10.1111/jdv.16892.
15. Sidbury R, Tom WL, Bergman JN, Cooper KD, Silverman RA, Berger TG, et al. Guidelines of care for the management of atopic dermatitis: section 4. Prevention of disease flares and use of adjunctive therapies and approaches. J Am Acad Dermatol. 2014;71(6):1218–33. doi: 10.1016/j.jaad.2014.08.038.