

▼ Dupilumab for atopic dermatitis

▼ Dupilumab (Dupixent - Sanofi-Aventis Groupe), a monoclonal antibody for the treatment of moderate-to-severe atopic dermatitis in adults who require systemic therapy, was licensed by the European Medicines Agency in September 2017. It is the first biological drug approved specifically for this condition. Here, we review the evidence for its efficacy and safety and consider its place in therapy.

Background

Atopic dermatitis (or atopic eczema) is a chronic, relapsing, inflammatory skin condition characterised by intense pruritus, dry skin, redness, inflammation and exudation, mainly affecting the flexor surfaces of the elbows and knees, the face and the neck.¹⁻³

It occurs more commonly in children but can also affect adults.⁴ In the UK, it is estimated to affect 20% of children and 8% of adults.⁵ Although the majority of patients with atopic dermatitis experience mild disease, around 2–4% of patients with atopic dermatitis present with a severe and extensive form, which interferes with daily activities, affects sleep and may have a significant impact on quality of life.^{1,6}

Treatment options

Standard topical treatment options include emollients, corticosteroids and calcineurin inhibitors (e.g. pimecrolimus and tacrolimus).^{2,6-9}

Emollients should be applied liberally and frequently as part of a daily skincare regimen.⁹ For moderate-to-severe disease they are thought to increase the efficacy of topical corticosteroids and have a steroid sparing action.^{7,8,10-12}

Topical corticosteroids are recommended for short-term use to control flares in patients who have failed to respond to regular use of emollients alone.^{7-11,13} The choice of topical corticosteroid potency depends on the severity of inflammation, the body area being treated and the patient's age.¹² Long-term use is not recommended as it can induce skin atrophy, dyspigmentation, acneiform eruptions and, if systemic absorption occurs, hypothalamic-pituitary-adrenal axis suppression.^{8,9,11,14}

Tacrolimus and pimecrolimus are suitable for patients whose condition has not been controlled by topical corticosteroids and who are at risk of adverse effects from long-term use of steroids.^{6,11} Moreover, tacrolimus and pimecrolimus can be applied to specific areas for which corticosteroids are more likely to induce skin atrophy (e.g. face, neck, flexural areas).^{3,9,10,14,15} Local skin reactions, skin infections such as folliculitis and herpes have been reported with their use.^{16,17} There have been post-marketing case reports of malignancies, including cutaneous and other types of lymphoma and skin cancers.^{16,17}

Systemic therapy is recommended for patients whose dermatitis is not adequately controlled by topical treatments, taking into account disease severity and its impact on quality of life.^{18,19}

Ciclosporin is licensed for patients with severe atopic dermatitis.²⁰ It can be used as a short-term treatment course (8 weeks) but longer courses (up to 1 year) may be required. Ciclosporin should only be prescribed following specialist advice and patients require regular monitoring (e.g. blood pressure, renal and liver function, serum lipids). Adverse effects include renal dysfunction, tremor, hirsutism, hypertension, diarrhoea, anorexia, nausea and vomiting as well as complications associated with immunosuppression.^{1,18,20,21}

The use of systemic corticosteroids is controversial, mainly because of their long-term toxicity and the severe flares that can occur

after treatment discontinuation.^{8,18,21} Their use should be reserved for short-term treatment (over a few weeks only) of acute, severe exacerbations.^{18,22}

Other systemic treatments such as azathioprine, methotrexate and mycophenolate mofetil are prescribed off-label to treat moderate-to-severe atopic dermatitis.¹ Phototherapy with ultraviolet B (UVB) radiation is also used for some forms of dermatitis.¹⁸

About dupilumab

Dupilumab is licensed for the treatment of moderate-to-severe atopic dermatitis in adults who require systemic therapy.^{14,23} It is a human monoclonal antibody that binds to the type I and II interleukin (IL)-4 receptor, specifically inhibiting IL-4 and IL-13 signalling. IL-4 and IL-13 are responsible for the inflammatory atopic response, are probably involved in the barrier dysfunction mechanism and are usually overexpressed during the acute phase of atopic dermatitis.^{7,23,24}

Dupilumab is administered by subcutaneous injection from a pre-filled syringe containing 300mg of dupilumab in 2mL. It is administered into the thigh or abdomen at a loading dose of 600mg (two 300mg injections), followed by a dose of 300mg given every other week.²³ It can be used as monotherapy or with concomitant topical corticosteroid treatment or, when necessary, with a topical calcineurin inhibitor.

If a patient does not respond adequately after 16 weeks of dupilumab, treatment discontinuation should be considered.²³ Patients with an initial partial response may subsequently improve with continued treatment beyond 16 weeks.

Evidence of efficacy

Evidence for the efficacy of dupilumab in adults with moderate-to-severe atopic dermatitis includes three randomised double-blind placebo-controlled studies. Two trials assessed short-term use (16 weeks) as monotherapy (SOLO1 and SOLO2).²⁵ The CHRONOS study included concomitant topical corticosteroids and lasted 52 weeks.²⁶ However, the primary efficacy outcome was assessed at week 16.

In all three trials, validated scales were used to define and assess disease severity (see Box 1).

The inclusion criteria were similar across the studies. Enrolled patients (n=2,119) had chronic, moderate-to-severe atopic dermatitis (Investigator's Global Assessment [IGA] score ≥ 3 and Eczema Area and Severity Index [EASI] score ≥ 16) that affected at least 10% of the body surface area, with moderate intensity pruritus. Patients had not been adequately controlled by previous treatments within 6 months before enrolment.^{14,25,26}

The SOLO1 and SOLO2 trials randomised 1,379 adult patients (mean age 38 years) with a history of chronic moderate-to-severe atopic dermatitis (mean duration >25 years) affecting approximately 50% of the body surface area (mean IGA score >3; mean EASI score=33; mean pruritus NRS score=7.4).^{23,25} Before enrolment, 33% of the patients had

Box 1: validated assessment scales²⁵⁻²⁹*Investigator's Global Assessment (IGA)*

A 5-point scale (0=clear; 3=moderate; 4=severe) of the clinical signs of erythema, infiltration, papulation, oozing and crusting.

Eczema Area and Severity Index (EASI)

A 72-point scale (0=clear; 0.1–1.0=almost clear; 1.1–7.0=mild; 7.1–21.0=moderate; 21.1–50.0=severe; 50.1–72.0=very severe) of the extent of the disease in four body areas (head/neck, trunk, upper limbs and lower limbs) and the clinical signs of erythema, induration/papulation, excoriation and lichenification.

Pruritus Numerical Rating Scale (NRS)

A 10-point scale (0=no itch; 10=maximum intensity itch) of the intensity of pruritus.

received systemic corticosteroids in the SOLO1 and SOLO2 trials and systemic immunosuppressant agents had been used by 25.9% and 31.4%, respectively.²⁵

The CHRONOS study randomised 740 adult patients (mean age 37 years) who had chronic atopic dermatitis (mean duration >25 years) affecting 55% of the body surface area and who had significant pruritus (average NRS=7.6); 53% of the patients had moderate disease (IGA=3) and 47% severe disease (IGA=4); the mean EASI score was 33.^{23,26} Before entering the study, 52.8% of patients had received systemic therapy, which included corticosteroids and immunosuppressants.¹⁴

In all the studies, two different dose regimens of dupilumab were evaluated. Patients received a loading dose of 600mg followed by 300mg every other week (licensed dose), or the loading dose followed by 300mg weekly, or placebo. All patients were allowed to use emollients twice daily.^{14,25,26}

The two co-primary outcomes were the proportion of patients with both an IGA score of 0 or 1 and a reduction of at least two points from baseline, and the proportion of patients who had an improvement of at least 75% on the EASI score (EASI-75) from baseline to week 16.^{14,25,26}

Dupilumab was superior to placebo, either when used as monotherapy or in combination with topical corticosteroids.^{14,25,26} As there was no difference between the weekly and alternate week maintenance dose,¹⁴ we have only reported the results for the licensed alternate week regimen.

Table 1: main results dupilumab vs. placebo^{25,26}

	SOLO1	SOLO2	CHRONOS	
	(week 16)	(week 16)	(week 16)	(week 52)*
IGA ≤1 and reduction ≥2 points	38% vs. 10% (p<0.001)	36% vs. 8% (p<0.001)	39% vs. 12% (p<0.0001)	36% vs. 13% (p<0.0001)
EASI-75	51% vs. 15% (p<0.001)	44% vs. 12% (p<0.001)	69% vs. 23% (p<0.0001)	65% vs. 22% (p<0.0001)
NRS reduction ≥4 points*	41% vs. 12% (p<0.001)	36% vs. 10% (p<0.001)	59% vs. 20% (p<0.0001)	51% vs. 13% (p<0.0001)

*secondary outcome.

A recently published study evaluated short-term (16 weeks) efficacy of dupilumab in combination with topical corticosteroids in 325 patients who were not adequately controlled with oral ciclosporin or were intolerant to it (65% of the study population), or for whom ciclosporin was contraindicated (35%).³⁰ Patients had chronic moderate-to-severe atopic dermatitis (mean EASI score=32; mean IGA score=3) affecting on average 55% of the body surface and with significant pruritus (mean NRS=6.7).

Overall, 62.6% of patients treated with dupilumab and 29.6% treated with placebo (p<0.0001) had an improvement of at least 75% on the EASI score from baseline to week 16 (primary outcome). An IGA score ≤1 and an IGA reduction of at least 2 points from baseline was achieved by 40.2% with dupilumab and 13.9% with placebo (p<0.0001). The intensity of itch was reduced by dupilumab (NRS score reduction of ≥4 points: 45.7% vs. 14.3%, p<0.0001).³⁰

Some limitations of the data

We are not aware of any studies that have compared dupilumab with ciclosporin. Only one trial evaluated the long-term efficacy of dupilumab (52 weeks) as a secondary outcome.²⁶ No data on disease-free period, maintenance of remission or rebound effects after treatment discontinuation are available.

Unwanted effects

The long-term safety data on dupilumab are limited and are based on the CHRONOS study. The overall rates of adverse effects were similar with dupilumab and placebo (88% vs. 84%, respectively) with 4% versus 5% classified as severe.²⁶ Discontinuation due to adverse effects was higher among patients treated with placebo (8%) than with dupilumab (2%). The most common adverse effects were infections (57% with dupilumab vs. 58% with placebo), mainly nasopharyngitis (23% vs. 19%) and eye disorders (31% vs. 15%), mainly conjunctivitis (14% vs. 8%).²⁶

Across the three main trials, conjunctivitis and other eye disorders (such as dry eye, eye pruritus and blepharitis) had a higher incidence among patients treated with dupilumab than with placebo (6.2% vs. 2.9%).¹⁴ Most cases were mild to moderate and self-limiting. Approximately 10–20% had not resolved by the end of the study.

After 52 weeks of treatment, the incidence of herpetic skin infections was similar (7% with dupilumab vs. 8% with placebo); however, patients treated with dupilumab reported a higher incidence of localised herpes simplex infections (6% vs. 3%).²⁶ All herpes viral infections resolved by the end of the study.¹⁴

A meta-analysis of eight clinical trials (phase 1–3 studies, 2,706 participants) evaluated the risk of infections in patients treated with dupilumab at any dose (range: 75mg to 300mg weekly).³¹ There was a reduced risk of skin infection (relative risk [RR] 0.54, 95% CI 0.42 to 0.70) and of eczema herpeticum (RR 0.34, 95% CI 0.14 to 0.84) with dupilumab compared with placebo.

No significant association between dupilumab and risk of infection was seen in patients enrolled in SOLO1, SOLO2 or CHRONOS trials (RR 0.98, 95% CI 0.83 to 1.16).³¹

Injection-site reactions occurred in 15% of patients treated with dupilumab and 8% of those receiving placebo.²⁶

After 52 weeks of treatment, the incidence of malignancy was 3.2% with dupilumab and 2.2% with placebo; the most commonly reported were benign lesions.¹⁴

Risk management plan

The risk management plan requested by the European Medicines Agency (EMA) includes a single-arm extension study in patients who have participated in previous dupilumab trials to assess immunogenicity (an important identified risk), risk of malignancies (an important potential risk) and conjunctivitis-related events after long-term exposure (up to 5 years) to dupilumab.¹⁴

A pregnancy outcomes database study and the institution of Pregnancy Registry aim to evaluate pregnancy outcomes in women exposed to dupilumab.¹⁴

Five trials are ongoing to evaluate the use of dupilumab in a paediatric population.^{14,32}

Cautions

Patients treated with dupilumab who develop conjunctivitis that does not resolve following standard treatment should undergo ophthalmological examination.²³

Caution is required in asthmatic patients, as the safety and efficacy of dupilumab have not been established.²³

Dupilumab may affect the immune response against helminth infections. If patients become infected while on treatment with dupilumab and do not respond to anti-helminth treatment, dupilumab should be discontinued until the infection resolves.²³

Use of live vaccines should be avoided; patients may receive inactivated or non-live vaccinations.²³

Costs

Drug	Dose	Cost/28 days
▼ Dupilumab	300mg every other week	£1,265
Ciclosporin	400mg daily*	£255

Costs based on prices in *Chemist and Druggist* and the *Drug Tariff*.

*based on a dose of 5mg/kg/day for an adult of 80kg.²⁰

What do guidelines recommend?

Guidance has not yet been issued by the National Institute for Health and Care Excellence, the Scottish Medicines Consortium or the All Wales Medicines Strategy Group.

Conclusion

Atopic dermatitis is a chronic skin condition characterised by intense pruritus, dry skin, redness, inflammation and exudation. Currently, the main topical treatment options include emollients, corticosteroids and calcineurin inhibitors. The only systemic treatment licensed for this condition is ciclosporin; however, its use is limited to short courses because of long-term toxicity.

▼ Dupilumab is a monoclonal antibody that is given by subcutaneous injection on alternate weeks. Its efficacy has been evaluated as monotherapy and in combination with a topical corticosteroid. Additionally, a short-term study evaluated its efficacy in patients who previously failed to respond to ciclosporin or who experienced ciclosporin toxicity or for whom ciclosporin was contraindicated. In all the studies, dupilumab produced statistically significant improvement in outcomes compared with placebo.

The most common adverse effects include nasopharyngitis, conjunctivitis, injection-site reactions and herpes simplex infection. Long-term safety data on dupilumab are limited and are based on a small number of patients.

Although dupilumab has produced improvements in the treatment of adults with moderate-to-severe atopic dermatitis, the lack of comparative trials with ciclosporin, limited data on long-term safety and efficacy, and its high price mean that its place in the management of atopic dermatitis is uncertain. It may provide an option for patients who do not respond to ciclosporin or for whom ciclosporin is contraindicated.

[R=randomised controlled trial; M=meta-analysis]

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