

Real-world effectiveness and tolerability of dupilumab in adult atopic dermatitis: a single-centre, prospective 1-year observational cohort study of the first 100 patients treated

DOI: 10.1111/bjd.19631

DEAR EDITOR, Dupilumab (Dupixent®) is the first biological drug to be licensed for the treatment of adults with atopic dermatitis (AD). Data regarding its long-term real-world effectiveness and tolerability are limited.

We report comprehensive outcome data at 1 year for the first 100 adult patients initiated on dupilumab in a specialist eczema clinic (May 2017–November 2019). In this prospective, observational cohort study (Health Research Authority UK ref.268527) all patients received dupilumab at the licensed dose. Wherever possible, patients on other systemic treatment(s) underwent a 4-week washout prior to dupilumab. In view of ophthalmic complications reported in trials, all patients were given preservative-free lubricating eye ointment prior to dupilumab.^{1–3} Disease activity and patient-reported outcome measures were assessed at baseline, week 12, week 24 and 1 year of treatment. Adverse events (AEs) were recorded and classified.⁴

The cohort ($n = 100$) included 63 men and 37 women [median age 40 years, interquartile range (IQR) 29–50; median body mass index 26.7 kg m^{-2} , IQR 23.4–29.9]. Patients had significant disease burden at baseline with high investigator- and patient-reported disease activity (Table 1), prevalent atopic comorbidities (80% atopic asthma; 72% allergic rhinitis; 58% allergic conjunctivitis; 53% food allergy) and prior exposure to multiple systemic treatments [mean (SD) 2.6 (1.1)]. There was also significant depression and/or anxiety (Table 1).

We saw early improvement in multiple outcome measures related to disease activity, quality of life, itch, depression and anxiety (Table 1). We saw continued improvement in patients who remained on dupilumab through to 1 year. For example, by 1 year, 63.3% of patients achieved at least a 75% improvement in Eczema Area Severity Index (EASI 75) relative to baseline. There was also marked improvement in psychological measures; only 6.6% of patients reported symptoms of moderate-to-severe depression or anxiety at 1 year vs. 37.9% and 33.7% at baseline, respectively. We observed a small but significant rise in mean peripheral eosinophil count at week 12, which normalized between week 24 and 1 year; serum IgE decreased progressively to 1 year (Table 1).

Ninety-four per cent of patients had experienced an AE by 1 year, with the majority considered mild or moderate. Six patients experienced a serious AE: death (unrelated to dupilumab; $n = 2$) or an AE requiring hospitalization (pneumonia; suicide attempt; depression with suicidal ideation; fracture; $n = 4$). Ophthalmic AEs were most common [29.3% of all AEs ($n = 76/259$); affecting 76% of patients]: predominantly allergic/dupilumab-associated conjunctivitis (32%), conjunctivitis (unspecified; 7%) or dry eyes (23%). Two of five cases of infective eye

disease were caused by herpes simplex virus (HSV). Median time to onset of ophthalmic AEs was 4 weeks (IQR 3–36). One patient paused dupilumab owing to severe allergic conjunctivitis but subsequently restarted with reduced dose frequency. There were similar rates of dupilumab-associated conjunctivitis in patients with or without pre-existing allergic conjunctivitis. The second most frequently reported AE was skin infection, including reactivation of HSV ($n = 18$), molluscum contagiosum ($n = 5$) and varicella zoster virus [VZV; $n = 1$ (no eczema herpeticum/disseminated VZV)]. All cases of molluscum pre-dated dupilumab, flared during treatment and then cleared by 1 year (as previously reported).⁵ Cutaneous AEs included eczema flare ($n = 22$; 14 cases localized to head and neck). Ten additional patients had persistent head and neck dermatitis/facial erythema. Of the 24 patients with head and neck dermatitis/facial erythema, one discontinued dupilumab owing to symptoms, eight resolved and 15 were ongoing at 1 year. There were five cases of injection site reaction. One patient developed guttate psoriasis (week 24) and discontinued dupilumab. Fourteen patients reported musculoskeletal symptoms, of whom six were diagnosed with enthesitis and/or inflammatory arthropathy by a rheumatologist (as previously reported).⁶ Four developed symptoms by week 12, with two late presentations (weeks 29 and 36). Two patients continued dupilumab with concomitant anti-inflammatories; one continued dupilumab at 4-weekly dosing with reduced symptoms; three discontinued dupilumab. Other AEs leading to discontinuation/pause of dupilumab comprised fatigue and arthralgia ($n = 1$ at week 12; discontinued); abdominal bloating ($n = 1$ at week 24; discontinued); and new neutropenia ($n = 1$ at week 24; stable after restarting).

We report long-term outcome data demonstrating the effectiveness of dupilumab in a large real-world cohort of adults with complex AD, with outcomes at 1 year (as observed) similar to trials.^{2–4} This is the first description of improvement in depression/anxiety in a real-world cohort. In comparison with trial data, we observed a higher incidence of AEs, including conjunctivitis, head and neck dermatitis and enthesitis/inflammatory arthropathy.^{2–4} Of note, our first 100 patients had significant atopic burden. Other real-world cohorts have also reported high/similar rates of ophthalmic AEs.^{7,8} We acknowledge the limitations of our study, including incomplete data and data presented 'as observed'. National registries and planned platform trials will characterize the comparative effectiveness and tolerability of dupilumab with other systemic therapies.

Acknowledgments: many thanks to the multidisciplinary team in the specialist adult eczema service, including consultants (E. Benton, H. Cookson, E. Higgins, F. Ferguson, S. Langan, B. Martin, E. Storan and S. Till), specialty trainees, nurse consultant (K. Jackson), research nurses (L. Griffiths, J. Gregory and M. Recter), clinical nurse specialists (A. Clery, J. Funa and J. Husaini), pharmacists (S. Guard and A. McGuire), database developer (T. Dasandi) and the King's College London IMPARTS team. Special thanks to Dr M. Turner, Clinical Psychologist in Dermatology, Guy's and St Thomas' NHS Foundation Trust, for review of the manuscript.

Table 1 Summary of disease outcome data at baseline, week 12, week 24 and 1 year of dupilumab

	Baseline	Week 12 ^a	Week 24 ^a	1 year ^a
Total number of patients	N = 100 ^b	N = 100 ^b	N = 97 ^{b,c}	N = 81 ^{b,d}
EASI score	n = 100	n = 97	n = 84	n = 79
Mean (SD)	19.9 (10.4)	7.2 (5.9)	5.6 (5.2)	4.7 (4.7)
Median (IQR)	17.5 (11.8–26.2)	5.2 (2.8–9.7)	4.2 (1.85–7.4)	3.0 (1.6–6.5)
Mean (SD) absolute change from baseline	–	–12.8 (8.5)	–14.7 (10.1)	–15.6 (10.5)
Patients who achieved		n = 97	n = 84	n = 79
EASI 100 (%)		3	4	4
EASI 90 (%)		10	24	29
EASI 75 (%)		37	55	63
EASI 50 (%)		75	82	86
Patients with IGA	n = 91	n = 86	n = 75	n = 58
Clear/almost clear (%)	0	29	36	52
Mild (%)	4	36	38	26
Moderate (%)	45	31	25	22
Severe (%)	50	3	1	0
Patients with PGA	n = 94	n = 93	n = 87	n = 65
Clear/almost clear (%)	5	44	31	55
Mild (%)	10	30	38	28
Moderate (%)	40	17	28	14
Severe (%)	45	9	2	3
POEM score (0–28)	n = 97	n = 92	n = 83	n = 76
Mean (SD)	19.5 (7.2)	8.6 (6.9)	8.3 (6.5)	6.1 (5.7)
Median (IQR)	20.5 (15.0–26.0)	7.5 (3–12.3)	6 (3–12)	4.5 (1.0–9.3)
Patients who achieved MCID ^e (%)	–	80	82	86
DLQI	n = 99	n = 96	n = 87	n = 78
Mean (SD)	15.0 (7.7)	6.4 (6.2)	6.0 (4.7)	4.3 (4.1)
Median (IQR)	15 (9.0–20.0)	5.0 (2–8)	5.0 (3–9)	3.0 (1–6)
Patients who achieved MCID ^e (%)	–	76	76 (n = 86)	85
Patients who achieved DLQI 0–1 (%)	–	21	16	31
1-week pruritus NRS	n = 74	n = 65	n = 58	n = 38
Mean (SD)	6.4 (2.5)	2.7 (2.4)	2.7 (2.6)	2.1 (2.2)
Median (IQR)	7 (5–8)	2.0 (1–4)	2.0 (1–4)	1.0 (0–3)
PHQ-9	n = 95	n = 94	n = 84	n = 76
Proportion of patients who scored > 10 (moderate-to-to-severe depression), n (%)	36 (37.9)	14 (14.6)	9 (16.1)	5 (6.9)
GAD-7	n = 95	n = 94	n = 83	n = 76
Proportion of patients who scored > 10 (moderate-to-to-severe anxiety), n (%)	32 (34)	17 (18)	13 (16)	5 (7)

(continued)

Table 1 (continued)

	Baseline	Week 12 ^a	Week 24 ^a	1 year ^a
Eosinophil count ($\times 10^9$ cells L ⁻¹)	n = 98	n = 94	n = 82	n = 79
Mean (SD)	0.54 (0.43)	0.8 (0.6)	0.6 (0.6)	0.6 (0.5)
Median (IQR)	0.45 (0.2–0.7)	0.6 (0.4–1.1)	0.4 (0.3–0.9)	0.4 (0.2–0.8)
IgE (UI mL ⁻¹)	n = 92	n = 61	n = 16	n = 18
Mean (SD)	12 432 (14 204)	8693 (9056)	7520 (7683)	5437 (5628)
Median (IQR)	6526 (2919–14 577)	4910 (2080–13 603)	4457 (1345–11 901)	2566 (1428–9965)

DLQI, Dermatology Life Quality Index (score 0–30); EASI, Eczema Area and Severity Index (score 0–72); GAD-7, Generalized Anxiety Disorder 7-item scale (score 0–21); IGA, Investigator Global Assessment (five-point scale); IQR, interquartile range; MCID, minimal clinically important difference; NRS, numerical rating scale (score 0–10); PGA, Patient Global Assessment (five-point scale); PHQ-9, Patient Health Questionnaire-9 (score 0–27); POEM, Patient-Orientated Eczema Measure (score 0–28). ^aActual mean (SD) interval for patient assessment from dupilumab initiation 12.2 (2.3) weeks, 26.8 (8.2) weeks and 50.3 (5.5) weeks, respectively. ^bDenominators for outcome measures indicated. ^cn = 97; three patients discontinued due to adverse events (AEs). ^dn = 81; patients discontinued due to an AE (n = 6), loss to follow-up (n = 3), comorbidities (n = 3) or death (n = 2). Eight were still due to attend the last visit. ^eThe MCID is 4 points for both POEM and DLQI.

A.V. Sears ¹, R.T. Woolf ¹, E. Gribaleva,^{1,2}
W. Abdelrahman,¹ S. Robbie,³ B. Menon,⁴ B. Kirkham,⁴
C.H. Smith ^{1,5} and A.E. Pink ¹

¹St John's Institute of Dermatology, Guy's and St Thomas' NHS Foundation Trust, London, UK; ²I.M. Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russian Federation; ³Department of Ophthalmology, Guy's and St Thomas' NHS Foundation Trust, London, UK; ⁴Department of Rheumatology, Guy's and St Thomas' NHS Foundation Trust, London, UK; and ⁵St John's Institute of Dermatology, School of Basic and Medical Biosciences, Faculty of Life Sciences and Medicine, King's College London, London, UK

Correspondence: Richard T. Woolf.

Email: richard.woolf@gstt.nhs.uk

A.V.S. and R.T.W. contributed equally.

References

- Simpson EL, Bieber T, Guttman-Yassky E et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. *N Engl J Med* 2016; **375**:2335–48.
- Blauvelt A, de Bruin-Weller M, Gooderham M et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. *Lancet* 2017; **389**:2287–303.
- de Bruin-Weller M, Thaçi D, Smith CH et al. Dupilumab with concomitant topical corticosteroid treatment in adults with atopic dermatitis with an inadequate response or intolerance to ciclosporin A or when this treatment is medically inadvisable: a placebo-controlled, randomized phase III clinical trial (LIBERTY AD CAFÉ). *Br J Dermatol* 2018; **178**:1083–101.
- Medical Dictionary for Regulatory Activities. Available at: <https://www.meddra.org/> (last accessed 8 January 2020).
- Storan ER, Woolf RT, Smith CH, Pink AE. Clearance of molluscum contagiosum virus infection in patients with atopic eczema treated with dupilumab. *Br J Dermatol* 2019; **181**:385–6.
- Willsmore ZN, Woolf RT, Hughes C et al. Development of inflammatory arthritis and enthesitis in patients on dupilumab: a case series. *Br J Dermatol* 2019; **181**:1068–70.
- de Wijs LEM, Bosma AL, Erler NS et al. Effectiveness of dupilumab treatment in 95 patients with atopic dermatitis: daily practice data. *Br J Dermatol* 2020; **182**:418–26.
- Faiz S, Giovannelli J, Podevin C et al. Effectiveness and safety of dupilumab for the treatment of atopic dermatitis in a real-life French multicenter adult cohort. *J Am Acad Dermatol* 2019; **81**:143–51.

Funding sources: none.

Conflicts of interest: conflicts of interest statements can be found in Appendix S1S1 (see Supporting Information).

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix S1 Conflicts of interest.