

needs of vulnerable groups with lower technological literacy. We call for active optimization of telehealth systems along with patient education to ensure usability for all.

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Reasons for discontinuation of dupilumab in adult atopic dermatitis in clinical practice

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DEAR EDITOR, Dupilumab, an anti-interleukin-4 α monoclonal antibody, has shown a positive benefit–risk ratio when treating moderate-to-severe atopic dermatitis (AD) in clinical studies.¹ High persistence for patients on dupilumab has recently been reported in a clinical practice setting, with 77% of patients remaining in treatment for 12 months in a retrospective study that included

1963 patients with AD; however, reasons for discontinuation were not investigated.² Investigating the reasons for treatment discontinuation in chronic diseases permits the assessment of both the safety and the effectiveness of a given treatment in a clinical practice setting. Our aim was to investigate the frequency and reasons for discontinuation of dupilumab in adults with AD, and the alternative subsequent treatment strategies.

We conducted a retrospective multicentric (16 tertiary referral hospitals) study in adult patients with moderate-to-severe AD for whom dupilumab was discontinued (defined as discontinuation $\geq$ 1 month) between March 2017 and September 2020.

From a total of 968 patients treated with dupilumab during the study period, 150 patients (15.5%) discontinued treatment after a median treatment duration of 5 months [interquartile range (IQR) 3–10]. Among the 150 patients who discontinued treatment, the main reasons for discontinuation were side-effect(s) in 61 patients (40.7%), lack of efficacy in 22 patients (14.7%), lack of efficacy and side-effect(s) in 23 patients (15.3%), planned pregnancy in 12 patients (8%), disease remission in six patients (4%) or various other reasons for 26 patients (17.3%). Among the six patients who stopped treatment owing to AD remission, the median duration of treatment was 57 weeks (IQR 44.25–65.25). One of these patients relapsed 6 months after discontinuation, requiring reintroduction of dupilumab. Side-effects that led to dupilumab discontinuation were, among others, ophthalmological side-effects (36 patients, 24%), facial erythema (12 patients, 8%), diffuse AD exacerbations (10 patients, 6.7%), asymptomatic eosinophilia (six patients, 4%), alopecia areata (four patients, 2.7%) and induced psoriasis (four patients, 2.7%) (Table 1). Although herpes infections were frequently reported as a side-effect, no patient stopped dupilumab treatment for this reason.

Patients with atopic comorbidities (allergic conjunctivitis and asthma) were more likely to discontinue dupilumab because of side-effects rather than lack of efficacy (44.3% vs. 9.1%). Demographic characteristics, such as age, sex, AD phenotype or age at initiation of dupilumab treatment were not associated with any particular reason for discontinuation. Treatment strategies after discontinuation of dupilumab were as follows: initiation of another systemic treatment (60 patients, 40%), topical treatments alone (45 patients, 30%) or reinitiation of dupilumab treatment (31 patients, 20.6%) (Table 1). For this latter strategy, the median time of dupilumab restart was 13 weeks (IQR 8–28), with a single 600-mg loading dose (15 patients, 48.4%) followed in the majority of cases (24 patients, 77.4%) by regular injections at 2-week intervals. Among the 31 patients who restarted dupilumab, full remission was observed in 13 patients (41.9%). In patients who stopped because of side-effects, and subsequently restarted treatment (five of 31 patients), the strategy was to gradually increase the dosage interval to between 3 and 8 weeks depending on the disease control in each patient. There was no recurrence of side-effects and the efficacy was maintained in three of five patients.

Table 1 Discontinuation of dupilumab in clinical practice and postdupilumab strategy

Discontinuation of dupilumab	N = 150, n (%)
Reason for discontinuation of dupilumab	
Adverse events	61 (40.7)
Adverse events plus lack of efficacy	23 (15.3)
Lack of efficacy	22 (14.7)
Pregnancy or plans of paternity	12 (8.0)
Remission	6 (4.0)
Others ^a	26 (17.3)
Side-effects leading to dupilumab discontinuation	
Ophthalmological side-effects ^b	36 (24)
Facial erythema	12 (8.0)
Diffuse AD exacerbation	10 (6.7)
Eosinophilia (> 500 mm ⁻³)	6 (4.0)
Induced psoriasis	4 (2.7)
Alopecia areata	4 (2.7)
Headaches	1 (0.7)
Injection site reaction	1 (0.7)
HSV infection	0 (0.0)
Others ^c	8 (5.3)
Postdupilumab strategy	
Systemic treatments	60 (40.0)
Ciclosporin	8 (5.3)
Methotrexate	34 (22.7)
Mycophenolate mofetil	2 (1.3)
Azathioprine	1 (0.6)
JAK inhibitor	11 (7.3)
Others ^d	4 (2.7)
Topical treatments only	45 (30.0)
Restarting of dupilumab	31 (20.6)
Phototherapy	3 (2.0)
Lost to follow-up	11 (7.3)

HSV, herpes simplex virus; JAK, Janus kinase. ^aOthers include noncompliance (n = 9), lost to follow-up (n = 4), COVID-19 (n = 3), surgery (n = 2), issues with insurance coverage (n = 3), wish of the patient (n = 2), suspicion of cutaneous lymphoma (n = 1), depression (n = 1) and uncontrolled asthma (n = 1). ^bConjunctivitis (n = 26), blepharitis (n = 4) and keratitis (n = 6). ^cAsthenia (n = 2), digestive symptoms (n = 1), genital erosive lichen planus (n = 1), anaphylaxis (n = 1), toxicoderm (n = 1), hepatitis (n = 1) and cutaneous lymphoma (n = 1). ^dApremilast (n = 1), clinical trial (n = 3).

Discontinuation of dupilumab owing to side-effects is rare in clinical trials (only 1.8% in a phase III trial including 110 patients with a follow-up period of 52 weeks).¹ However, a previous clinical practice setting study from 2018, conducted in 241 patients, reported a discontinuation frequency of 17.4%, which was similar to that found in our study, and 11.3% when discontinuation was the result of side-effects after 1 year of use.³ Conjunctivitis is a frequently reported side-effect in clinical trials (3.6–11.8%).^{1,4,5} In a clinical trial with a 76-week follow-up, three of 1491 patients (0.2%) discontinued dupilumab owing to conjunctivitis.⁶ We report discontinuation frequency of 3.7% owing to ophthalmological side-effects in a clinical practice setting. One limitation of our study is that we had no

information about the patients who continued dupilumab, thus drug survival analysis could not be conducted.

Approximately 3 years after the approval of dupilumab for AD treatment in France, our study shows an overall frequency of discontinuation owing to side-effects (mostly ophthalmological) of 8.7%. We report that discontinuation of the drug for complete remission is currently rare in adults, although common practices vary when disease remission occurs, including adjustment of the dose-spacing regimen or permanent discontinuation of dupilumab. Further studies are needed to determine the relapse rate after cessation of dupilumab treatment. Our results underline the importance of clinical practice studies in assessing the benefit–risk ratio of systemic treatments in AD.

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Data availability: the data that support the findings of this study are available from the corresponding author upon reasonable request.

Supporting Information

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

File S1 Full list of affiliations.

Sustainability in skin cancer surgery

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DEAR EDITOR, Carbon emissions ascribed to medical instruments account for one of the largest proportions of the National Health Service (NHS) carbon footprint.¹ Our aim was to evaluate the sustainable value of the main types of theatre packs used for skin surgery (single-use and reusable) based on their economic, environmental and social sustainability, and determine which is more sustainable for long-term use.

Data on the number and types of packs were collected over a 4-week period in 2019 in the Dermatology Department, University Hospital of Wales. The results were used to calculate a mean value for the number of times each pack type was used on an average week at the department. The calculations for the cost and carbon footprint of each pack type per week were based on those values accordingly. The price of the single-use packs was acquired from the manufacturing company and the cost of disposal was provided by the health board's waste management manager according to the pack weight and the waste treatment process (incineration). The cost of using the reusable packs was determined by the cost of the instruments, sterilization process, blue sterilization wrap disposal, and staffing (time taken to arrange the instruments post-procedure and transportation of packs to the sterilization

unit). The carbon footprint resulting from the life cycle of each pack type was determined using published emissions factors for the production of the raw materials used to manufacture the components of the pack (i.e. instruments, plastic cover, plastic tray and gallipot) and for disposal. Additionally, the carbon footprint of the sterilization process for reusable packs was estimated using published data on water and electricity consumption.² Emissions from the transport of waste to the energy recovery facility were not included.

On average, 62 packs are used for skin surgery per week (14 single-use, 48 reusable). The cost of a single-use pack is £20.57 vs. £13.35 for a reusable pack (Figure 1a). The amount of greenhouse gas (GHG) emissions caused by the use of each single-use pack is 1.436 kgCO₂eq (kilograms of CO₂ equivalents) compared with 1.121 kgCO₂eq for a reusable one (Figure 1b). Extrapolating from the values obtained for the cost and GHG emissions of the two pack types, on the basis that 14 single-use and 48 reusable packs are used per week, the total amount of money spent on theatre packs is £974.22/week (£50 659.54/year) and the total carbon footprint generated is 73.903 kgCO₂eq/week (3842.932 kgCO₂eq/year). The figures presented here have been rounded and also include transport costs of the re-usable packs to the sterilization unit, calculated on a weekly or yearly basis and not per pack. A full breakdown of these figures is available from the corresponding author on request.

This study is the first to compare the sustainability of single-use and reusable packs for skin surgery, accounting for the costs and GHG emissions from the life cycle of each pack type. Measuring the carbon footprint of various elements of healthcare services should be integrated into service evaluations and quality improvement to sustain their delivery. In a 2018 report, medical instruments were identified as one of the biggest contributors to the NHS carbon footprint, comprising over 13% of its total emissions.³ Therefore, opting for the most sustainable type of instruments minimizes the costs and associated GHG emissions. Our findings demonstrate that reusable packs are more sustainable due to their reduced cost and GHG emissions. If our department were to switch to using only reusable packs, it would lead to a saving of £101.03/week or £5253.55/year and lower the annual GHG emissions by ~6% (229.205 kgCO₂eq), which is equivalent to a 2-h flight. It is likely that this is an underestimate because sterilization energy data are from Australia, where coal provides most energy while our hospital sources energy from renewable sources.

Limitations include that this is a single-centre study and that the GHG emissions from the production and disposal of the packs were calculated using estimates of the instruments' weights and amounts of raw materials used to manufacture them, and empirical assumptions regarding the instruments' lifetimes. Consequently, the carbon footprint data for each pack type may be subject to a slight degree of imprecision. Furthermore, the patient outcomes and social sustainability of both pack types were not determined; however, a questionnaire has been piloted for this purpose and the pilot data will shape a larger study to address these objectives.