Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a critical appraisal

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Summary

Aim:

Blauvelt *et al.* (*The Lancet* 2017; **389**: 2287-303) aimed to compare the long-term efficacy and safety of dupilumab with medium-potency topical corticosteroids (TCS) versus placebo with TCS in adults with moderate-to-severe atopic dermatitis (AD).

Setting and design:

This multicentre randomised, double-blinded, placebo-controlled trial was conducted in hospitals, clinics and academic institutions across 161 sites in 14 countries.

Study exposure:

Adults with moderate-to-severe AD were randomly assigned (3:1:3) to receive subcutaneous dupilumab 300mg once weekly (qw) plus TCS, dupilumab 300mg every 2 weeks (q2w) plus TCS, or placebo plus TCS until week-52.

Primary outcome measures:

Co-primary efficacy endpoints were patients (%) achieving Investigator's Global Assessment (IGA) 0/1 and 2-points or higher improvement from baseline, and Eczema Area and Severity Index 75% improvement from baseline (EASI-75) at week-16.

Results:

740 patients were included in the trial: 319 were randomly assigned to dupilumab qw, 106 to dupilumab q2w and 315 to the placebo arm. At week-16, more patients in the dupilumab groups achieved the co-primary endpoints: IGA 0/1 (39% [125 patients] qw dosing, 39% [41 patients] q2w dosing vs 12% [39 patients] receiving placebo; $p<0.0001$) and EASI-75 (64% [204] and 69% [73] vs 23% [73]; $p<0.0001$). Whilst no new safety signals were identified, adverse effects (AEs) were noted in 261 (83%) in those receiving dupilumab qw plus TCS, 97 (88%) dupilumab q2w plus TCS and 266 (84%) for placebo plus TCS. Rates of conjunctivitis,

injection site reactions and local herpes simplex infections were higher in the dupilumab groups compared with placebo.

Conclusions:

Blauvelt *et al.* concluded that dupilumab treatment added to TCS improved AD up to week-52 compared with TCS alone, and also demonstrated acceptable safety.

Comment

What is already known about this topic?

Atopic dermatitis (AD, syn. eczema, atopic eczema) is a chronic, pruritic inflammatory skin disorder primarily affecting children, but sometimes persisting, re-emerging or starting in adulthood with an estimated world prevalence in adults of 2-11.5%.[1-3] Severe disease can be very disabling and has been associated with chronic pruritus, sleep disturbance, reduced quality of life, anxiety and depression.[4,5]

Most cases of AD typically respond well to appropriate use of emollients plus topical anti-inflammatory treatments (TCS and/or topical calcineurin inhibitors [TCI]), but severe disease and some cases of moderate disease may require longer term potent TCS. This could lead to side-effects such as skin thinning if used inappropriately, e.g. due to continued use on sensitive sites such as the face. Narrowband UVB phototherapy is an established adjunct in the treatment of moderate-to-severe AD.[6] Systemic immunosuppressive medications are usually reserved for chronic severe AD not responding to other treatments. Ciclosporin remains the only licensed treatment for refractory AD in many European countries. Studies have shown a mean clinical improvement between 53% and 95% using different clinical severity scores after short-term treatment, however prolonged use is associated with hypertension, renal impairment and a possible increased risk of cancer.[7-15] Evidence for other

systemic immunosuppressant treatment is more limited, but methotrexate (mean SCORAD [SCORing of Atopic Dermatitis] improvement: 42%; SCORAD 50% improvement from baseline [SCORAD-50]: 40%), azathioprine (mean SCORAD improvement: 39%; SCORAD-50: 45%) and mycophenolate (shown to be equally effective as ciclosporin in one small study but without data on SCORAD % improvement from baseline values) are also used.[6,8,16-20] Evidence for effectiveness of current systemic treatments in severe AD is modest and monitoring is required due to the risk of AEs.[8] Development of more efficacious treatments for severe AD with a better safety profile is therefore welcome, especially if shown to be cost-effective.

Dupilumab is the first US Food and Drug Administration (FDA)-approved biologic treatment for moderate-to-severe AD and is a fully human monoclonal antibody. It binds to the alpha subunit of the interleukin-4-receptor, which inhibits signalling from interleukin-4 and interleukin-13.[21] Aside from AD, its efficacy and safety have been demonstrated in patients with other atopic conditions, including asthma and chronic rhinosinusitis.[22,23] Simpson *et al.* demonstrated short-term efficacy at week-16 in patients with moderate-to-severe AD (IGA 3-4) in two placebo-controlled randomised trials (SOLO 1 and SOLO 2) but did not assess longer term outcomes.[24] The LIBERTY AD CHRONOS trial aimed to provide evidence on long-term efficacy and safety of dupilumab at a dose of 300mg given once weekly or every 2 weeks in adults with moderate-to-severe AD up to 52 weeks in a phase 3 randomised trial.[25]

Strengths of the research

This is the first study to assess long-term efficacy and safety of dupilumab treatment for moderate-to-severe AD in adults and the authors are to be commended for conducting an appropriate length study in such a chronic disease that requires long-term maintenance treatment for disease suppression.

In contrast to the SOLO 1 and 2 studies, patients were advised to continue regular use of topical treatments where required (TCS or TCI if use of TCS was inadvisable) in both active and placebo arms. The authors suggested that use of TCS/TCI provided a more pragmatic approach, aiming to mirror standard care. The range of secondary outcomes are sufficient in this study and include a variety of important clinician and patient-reported measures.

As expected with a publication in *The Lancet*, the study is well reported with good adherence to CONSORT guidelines,[26] including: (i) a clear abstract which includes the study aim and relevant outcomes, (ii) clearly described settings and methodology, expanded in the appendix, (iii) use of a table to display baseline characteristics, and (iv) a CONSORT flow diagram to show the phases of parallel groups from screening through to study completion. The trial was pre-registered on ClinicalTrials.gov. The study was industry sponsored and the funder participated in the design, analysis, drafting, revision, and approval of the submitted paper. Conflicts of interest were declared for all 31 authors, 16 of whom had a financial conflict with the commercial sponsors.

Assessment of validity

Internal validity

We used the Cochrane risk of bias framework to assess internal validity.[27]

Randomisation (selection bias)

Patients were randomised in a ratio of 3:1:3 to dupilumab 300mg qw +TCS; dupilumab 300mg q2w +TCS; placebo +TCS, respectively using a central randomisation scheme that was provided by an interactive voice/web response system which ensures allocation concealment and minimises risk of selection bias. The patients were stratified by baseline disease severity

and geographical location ensuring uniformity between groups. Although details on the method of random sequence generation were not given, the method used was likely to have been robust and consequently we determined the risk of selection bias to be low.

Blinding (performance bias and detection bias)

The study design included adequate blinding to patients, study personnel and outcome assessors, until the pre-specified unblinding following a database lock. The authors state that the statistician who provided the randomisation sequence was unblinded. We are uncertain of the significance of this without further information: in theory, the integrity of the trial could be threatened if the statistician was not external to the sponsors and was involved in discussions about changes in trial design while the trial was ongoing. The authors describe identical study drug kits and protocols for the 3 study arms, and the placebo syringes were identical to the dupilumab syringes, minimising the risks of any performance and detection biases, which we rated as low overall.

Intention to treat (attrition bias)

Intention to treat (ITT) analysis was used for the co-primary binary endpoints. The authors stated that patients were recorded as non-responders after rescue treatment initiation or study withdrawal. At week-16, when the co-primary endpoints were assessed, there were very few dropouts across groups, resulting in a low risk of attrition bias for these outcomes. By week-52 however, there was a higher proportion of dropouts in the placebo group (33% vs 14% and 15% dropout rate in the two active dupilumab groups). The authors suggest that higher dropouts in the placebo group may be related to increased satisfaction with dupilumab treatment.

Continuous efficacy endpoints were analysed by multiple approaches including the last observation carried forward (LOCF) method with an analysis of covariance (ANCOVA) model (a statistical tool that sits between analysis of variance and regression analysis). Additional sensitivity analyses were performed and detailed in the appendix, including a multiple imputation approach with ANCOVA (continuous endpoints) and post-baseline LOCF (binary endpoints). Imputation refers to a statistical method used to estimate missing outcome data using other available data to infer the missing values and conform to ITT.[28] All these analyses supported the results from the primary analyses; therefore, we judged the overall risk of attrition bias as low.

Selective reporting (reporting bias)

All the outcomes stated in the trial register (published before the start of the study, ClinicalTrials.gov ID NCT02260986) were reported in the final publication and we have rated the risk of reporting bias as low. However, one deviation was noted whereby *The Lancet* publication reports on two co-primary endpoints whereas only the IGA endpoint was registered on ClinicalTrials.gov as a primary endpoint. Although no explanation is given in the article or trial register for the apparent deviation, the published study protocol reports that the European Union and Japanese centres had requested that EASI-75 was added as a co-primary endpoint. The European Clinical Trials Register (EudraCT number 2013-003254-24) recorded both endpoints as co-primaries.

Power

The sample size calculation estimated that 300, 100 and 300 patients in the dupilumab 300mg qw, dupilumab 300mg q2w and placebo groups would be needed, respectively. Further

details, presented in the appendix, explained that the study provided 99% power to detect a difference of 29% in the IGA primary endpoint for comparisons between dupilumab groups and placebo. Although the accompanying appendix stated that the sample size was chosen to "enable adequate characterization of the long-term safety profile" (without giving further details), the very high power of 99% (normally set at 90%) seems excessive, as there are ethical concerns about a study that is unnecessarily large. The authors also state that the study was not powered to compare endpoints between the two dupilumab groups, which begs the question of why two dupilumab groups were tested in this study?

The power calculation was based on comparing the primary endpoints at week-16, using results from a previous phase 2 dupilumab study.[24] It could be argued that the study should have been powered to detect differences at 52 weeks as the authors stated the study rationale was to assess long-term efficacy and not efficacy at 16 weeks. No adjustment for the level of statistical significance is reported for the introduction of the additional primary outcome following trial registration.

External Validity

The study population included adults with moderate-to-severe AD (diagnosed by American Academy of Dermatology Consensus Criteria)[29] with an "inadequate response to medium-potency to high-potency TCS (with or without TCI as appropriate)". This was defined further in the appendix where it stated it represents: "failure to achieve and maintain remission or a low disease activity state… despite treatment with a daily regimen of TCS of medium to high potency, applied for at least 28 days or for the maximum duration recommended by the product prescribing information (e.g. 14 days of super-potent TCS)". How this definition (which could include someone with moderate AD who failed to achieve low disease activity

after using only a medium potency TCS for 28 days) was operationalised i.e. whether all potential study patients were given a "proper" course of TCS treatment, or whether it was a subjective decision left to the discretion of the paid recruiting doctor is not clear. In practice potent and super-potent TCS are often used for longer periods than described in this study.[30]

Over half (53%) of study patients had moderate AD (IGA 3) and given that systemic treatment is usually reserved for *severe* cases who have the greatest unmet clinical need, we question the rationale for including moderate disease at all. A large number of private dermatology clinics were involved in recruiting to the study (investigators and sites detailed in the appendix), and this may explain why moderate AD patients make up the majority. The inclusion of this large proportion of moderate AD patients may also explain the significant improvement in endpoints observed in the placebo arm, above what might normally be expected in an AD trial of those with severe disease.

We believe the inclusion of such a large proportion of moderate AD patients impacts significantly on the study's external validity and whether it really addresses the correct population who require biologic treatment in clinical practice. It is worth noting that patients with moderate AD represent a much larger potential market for the manufacturers. As a minimum, we would have expected a planned subgroup analysis of the moderate and severe patients separately, but unfortunately this was not the case, and no post-hoc subgroup analysis was shown - data that we and guideline writers would need before recommending such a systemic treatment for those with severe disease.

A large number of outcomes were measured in this study, covering all of the core outcome domains agreed by the international Harmonising Outcome Measures in Eczema (HOME) initiative, namely "clinical signs (physician assessed)", "symptoms (patient assessed)", "quality of life" and "long-term control of disease".[31] The measures used to assess

these domains include the core outcome measures agreed by the HOME initiative: EASI and POEM (patient oriented eczema measure). The authors are to be commended for including such core outcomes which will facilitate comparability of this study in a meta-analysis with others that use core outcomes. The EASI score, a well validated and sensitive objective AD outcome measure,[32] assesses the severity and extent of: erythema; induration; papulation and oedema; excoriations; and lichenification with a score ranging from 0 to 72. The use of the IGA as a co-primary endpoint should be interpreted with caution as it is limited by lack of standardisation and no consideration of disease extent (e.g. no body surface area).[33] However the authors can be forgiven as the FDA recommends the use of such an unvalidated global assessment as the primary endpoint for new drug approval trials in AD for reasons that are unclear; hence its almost universal use in dermatology trials in the US.[33]

In assessing long-term disease control, the study recorded objective and subjective outcomes at 4 weekly intervals, proportion of topical and systemic rescue medication-free days and incidence rate of flares (defined as worsening of AD requiring escalation or intensification of treatment). There are inherent challenges in studying a chronic, intermittent disease such as AD and consequently defining long-term disease control is difficult, with no widely accepted or validated measure[34] – a challenge that is currently being addressed by the HOME group.

Other issues

The authors may have introduced some subtle "framing bias" through the way in which systemic medications were referred to negatively with comments such as their "long-term use…is not recommended, due to risk of serious toxicities"- with little evidence backing this

up. It is true that existing systemic treatments for AD require monitoring, but most appear safe when used in adherence to treatment guidelines.[8]

There was also an impressive number of centres and principal investigators involved across multiple continents (161 sites in 14 countries). Whilst this may have helped maximise recruitment activity, such an approach, along with concerns that the study might have been overpowered at 99% rather than the conventional 90%, raises concerns that some degree of "seeding" was planned with this study. Seeding refers to the testing of a drug in a large number of centres and countries in order to promote confidence and familiarity in the study drug; in the hope that clinicians endorse the drug following study completion.[35]

Although the study design was robust, we have to question why there was no active comparator group given that safety and efficacy for dupilumab has already been demonstrated in two placebo-controlled studies.[24] Is this a fair test of a new biologic? We are not convinced it is. We were also disappointed to see no planned active comparator trials when we searched the main trial register (www.ClinicalTrials.gov, accessed 2nd October 2017). If regulatory bodies such as the National Institute for Health and Care Excellence (NICE) are going to assess dupilumab, they will want to see evidence of how it compares with existing systemic treatment (in terms of an unbiased estimate of efficacy, safety, convenience and cost-effectiveness). However, given that it is not in industry's interests to take the risk of evaluating comparative efficacy and cost-effectiveness against cheaper active comparators,[36] it is likely that we will have to wait for a non-industry sponsored study before dupilumab's true comparative efficacy, safety and cost against the other systemic drugs are known. Network meta-analysis is another approach that might be used in the meantime.[37]

Overall assessment (including any potential application of the research to clinical practice)

This study reinforces the 16-week efficacy and safety outcomes from SOLO 1 and 2 and goes further to demonstrate maintained efficacy and safety up to week-52 of treatment. The findings demonstrate dupilumab was generally well tolerated in this study with no new safety concerns. It is however too early to determine rarer AEs, which may be picked up during ongoing monitoring after its licence.[38] This study confirmed a strong association of dupilumab with conjunctivitis, occurring in 17.9% of treated patients. This was mild in the majority of cases and appears to be specific to AD as it has not been identified in other conditions treated with dupilumab.[22,23] Patients should be closely monitored to detect this at an early stage, in particular those with more severe symptoms.

Our appraisal has shown that the risk of bias appears to be low in this study with no major concerns regarding internal validity. Our major concerns resided with the external validity of the study - the inclusion of AD patients with moderate disease and the lack of subgroup analysis for those with severe AD where most interest in systemics reside. We also feel uncomfortable about the ethical rationale of asking patients with "an inadequate response to topical corticosteroids" to be randomised to a control group of TCS plus placebo for a whole year. Whilst continued use of TCS better reflects real-world practice, it was surprising that patients on weekly dupilumab were still requiring TCS or systemic rescue therapy 66.3% (100 minus 33.3%) of the time over 52 weeks. It may be argued that the whole point of using systemics is to be free of the daily toil of applying topical therapies. We calculated the number needed to treat (NNT) for dupilumab as 3.7 (39% achieved IGA 0/1 vs 12%) which is a reasonable magnitude of benefit for patients receiving this drug, although it needs to be borne in mind that the study drug was compared against placebo rather than an active comparator, and few of us use placebo injections in clinical practice.

It is unfortunate that despite testing two different dupilumab dose regimens (300mg once weekly or every 2 weeks) which produced very similar results, the authors remained silent on which regimen would be preferred. Thankfully, the clear reporting of the study accompanied by the large study power allows us to estimate and interpret these differences for ourselves. For the outcome of IGA 0/1 at week-16, the difference in proportions between dupilumab once weekly and every 2 weeks was 0.5% in favour of once weekly (39.18% minus 38.68% i.e. trivial difference), with a corresponding 95% confidence interval with continuity correction of -10.82% (i.e. every 2 weeks up to 10.82% better) to +11.25% (i.e. once weekly up to 11.25% better). For EASI-75, the difference in proportions between dupilumab once weekly and every 2 weeks was 4.92% *in favour of dupilumab every 2 weeks* (68.87% minus 63.95%), with a 95% confidence interval ranging from -6.22% in favour of once weekly to +15.03% in favour of every 2 weeks. We conclude that dupilumab used every 2 weeks is probably just as effective as when it is used once weekly, but at half the cost and potentially less long-term toxicity.

On the whole, the authors should be praised for their study conduct and reporting, which demonstrated longer term benefit and safety of dupilumab. Clinicians such as ourselves welcome further treatment options with good efficacy and few side-effects for managing severe AD, particularly in cases where other systemic treatments have failed. What is now needed are studies that compare dupilumab against existing systemic treatments such as methotrexate in people with severe AD or for those who have failed on phototherapy and one other systemic. Longer term data beyond one year will also be important for patients entering into this length of treatment as it is not clear whether dupilumab needs to be continued indefinitely or whether it can be stopped or used intermittently to maintain

remission, and whether such long-term strategies will be safe. Cost-effectiveness has also received little attention so far and we welcome modelling of such data by bodies such as NICE.

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