



After the approval of dupilumab for moderate-to-severe atopic dermatitis: what is next on the research agenda?

DOI: 10.1111/bjd.16505

Linked Article: de Bruin-Weller et al. *Br J Dermatol* 2018; **178**:1083–1101.

About 15 years after the introduction of the first biological therapies for psoriasis, the approval of dupilumab for the treatment of atopic eczema is considered by many affected patients, their families and dermatologists around the world to be the beginning of a new era in the clinical care of this burdensome disease. The U.S. Food and Drug Administration granted the application for dupilumab a breakthrough therapy designation,¹ and thus by definition² declared atopic eczema to be 'a serious or life threatening disease or condition', and confirmed that 'preliminary clinical evidence [concerning dupilumab for atopic eczema] indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints'.

When dupilumab was approved in the U.S.A. a total of 2119 adult participants with moderate-to-severe atopic dermatitis not adequately controlled by topical treatment had been investigated in three placebo-controlled trials.¹ These three trials included more patients than all previous trials investigating systemic treatments for severe atopic eczema. In comparison, 1653 patients in total were included in 34 randomized controlled trials on other systemic treatment options for moderate-to-severe atopic eczema summarized in a systematic review.³ Thus, external evidence from placebo-controlled trials concerning the clinical efficacy of dupilumab is substantially stronger than trial evidence for all other systemic agents used for atopic eczema such as ciclosporin, azathioprine, methotrexate, mycophenolate and systemic glucocorticosteroids.^{3–7}

In the current issue of the *BJD*, de Bruin-Weller et al.⁸ present comprehensive results of a placebo-controlled randomized phase III clinical trial on the safety and efficacy of dupilumab with concomitant topical corticosteroids in adults who had previously not responded to ciclosporin or in whom ciclosporin was medically inadvisable. About two-thirds of all patients included were previously exposed to ciclosporin, with inadequate efficacy and important side-effects being the most frequent reasons for ciclosporin discontinuation. In < 5% of all patients included, ciclosporin worked well prior to trial enrolment. An important research question for future trials is thus the comparative efficacy of ciclosporin vs. dupilumab.

The primary outcome of the trial was $\geq 75\%$ improvement in the Eczema Area and Severity Index (EASI) at week 16 compared with baseline. Both dupilumab dosages (300 mg

weekly and 300 mg every other week) were significantly more efficacious than placebo in the primary outcome, as well as all secondary outcomes. The mean weekly dosage of topical corticosteroid use was also lower in dupilumab-treated patients than in the placebo group. I was very happy to see that the study adhered to the recommendations of the international Harmonising Outcome Measures for Eczema (HOME) initiative by including the EASI as the measurement of clinical signs of atopic eczema, the Patient-Oriented Eczema Measure to assess eczema symptoms, and an assessment of the impact of health-related quality of life.^{9–11} The adherence to consented core outcome sets is one crucial step towards making trial evidence more relevant for patients and guideline developers, and for clinical decision making.¹² It is therefore very positive that the other dupilumab trials^{4–6} also assessed the core outcome domains clinical signs, disease symptoms and quality of life. The fourth core outcome domain, long-term control of flares, needs to be included in future trials after the HOME group reached consensus on the best way to define and measure this outcome domain.^{11,13}

After the approval of dupilumab and documentation of its efficacy in placebo-controlled trials, important next steps in the research agenda include long-term comparative effectiveness studies, safety studies with large numbers of patients, and real-world health economic investigations. In addition to these standard topics for the research agenda, modern information technology and emerging new public health concepts suggest additional research priorities. Patient-reported outcomes such as quality of life are being increasingly used in routine care not only as an outcome (which is the only use in clinical trials), but also for diagnostic and monitoring purposes in individual clinical decision making.¹⁴ In oncology it was shown that the systematic electronic real-time use of patient-reported assessments in routine care is associated with higher survival rates.¹⁵ Electronic patient-reported symptom monitoring may also be an effective way to improve the medical care of patients with atopic eczema and other chronic skin diseases and should therefore be subject to future investigations.

After the approval of dupilumab as the first biologic for atopic eczema and the expectation of more specific drugs in the near future, additional research questions should be posed. These include the definition of adequate indication and appropriateness criteria, recommendations for treatment duration and discontinuation of biological therapy, reasons for physicians to recommend new or conventional therapies, and the development of evidence-based patient information material and decision aids.

Another emerging research topic not only for atopic eczema relates to the digital revolution we are currently facing. Driven by more and more powerful information technology,^{16–18} predictive modelling and learning computer algorithms, individualized care and precision medicine no longer appear to be a vision, but rather a realistic scenario to be reached in the near future. We probably all agree that the rapidly increasing data from electronic health records, administrative datasets and molecular biology offer many new options for research and individualized care. However, such routine care data have to be considered as exploratory and much more prone to bias than data from controlled research, and therefore the results of such approaches should be interpreted with caution. An important future challenge to development models will be effective integration of this rapidly increasing routine care data – which can be considered as a sort of ‘collective internal evidence’ – with best evidence from clinical trials and individual patient preferences.

Inspired by the psoriasis registries and the German atopic eczema registry TREATgermany,¹⁹ several national atopic eczema registries are currently being started or planned in Europe and beyond. The cooperation of the different national eczema registries and the a priori harmonization of data collection across registries²⁰ offer a unique chance to work together efficiently and collaboratively through the research agenda for moderate-to-severe atopic eczema to optimize further the clinical care of patients with this common condition.

Conflicts of interest

J.S. is coprincipal investigator of the German Atopic Eczema Registry TREATgermany. He has received institutional research grants for investigator-initiated studies from Novartis, Pfizer, MSD, ALK and Sanofi.

Centre for Evidence-Based Healthcare,
Medizinische Fakultät Carl Gustav Carus,
TU Dresden, Fetscherstraße 74, 01307
Dresden, Germany
E-mails: Jochen.Schmitt@uniklinikum-dresden.de

J. SCHMITT

References

- 1 U.S. Department of Health Human Services. FDA approves new eczema drug Dupixent. Available at: <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm549078.htm> (last accessed 26 February 2018).
- 2 U.S. Department of Health Human Services. Fact sheet: breakthrough therapies. Available at: <https://www.fda.gov/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendments/totheFDCA/FDASIA/ucm329491.htm> (last accessed 26 February 2018).
- 3 Roekevisch E, Spuls PI, Kuester D et al. Efficacy and safety of systemic treatments for moderate-to-severe atopic dermatitis: a systematic review. *J Allergy Clin Immunol* 2014; **133**:429–38.
- 4 Beck LA, Thaci D, Hamilton JD et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. *N Engl J Med* 2014; **371**:130–9.
- 5 Thaci D, Simpson EL, Beck LA et al. Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial. *Lancet* 2016; **387**:40–52.
- 6 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.
- 7 Schmitt J, Schmitt N, Meurer M. Cyclosporin in the treatment of patients with atopic eczema – a systematic review and meta-analysis. *J Eur Acad Dermatol Venerol* 2007; **21**:606–19.
- 8 de Bruin-Weller M, Thaci D, Smith CH et al. Dupilumab with concomitant topical corticosteroid treatment in adults with atopic dermatitis with an inadequate response or intolerant 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**:1083–1101.
- 9 Spuls PI, Gerbens LAA, Simpson E et al. Patient-Oriented Eczema Measure (POEM), a core instrument to measure symptoms in clinical trials: a Harmonising Outcome Measures for Eczema (HOME) statement. *Br J Dermatol* 2017; **176**:979–84.
- 10 Schmitt J, Spuls PI, Thomas KS et al. The Harmonising Outcome Measures for Eczema (HOME) statement to assess clinical signs of atopic eczema in trials. *J Allergy Clin Immunol* 2014; **134**:800–7.
- 11 Chalmers JR, Simpson E, Apfelbacher CJ et al. Report from the fourth international consensus meeting to harmonize core outcome measures for atopic eczema/dermatitis clinical trials (HOME initiative). *Br J Dermatol* 2016; **175**:69–79.
- 12 Williamson PR, Altman DG, Bagley H et al. The COMET Handbook: version 1.0. *Trials* 2017; **18**:280.
- 13 Chalmers JR, Schmitt J, Apfelbacher C et al. Report from the third international consensus meeting to harmonise core outcome measures for atopic eczema/dermatitis clinical trials (HOME). *Br J Dermatol* 2014; **171**:1318–25.
- 14 Trautmann F, Hentschel L, Hornemann B et al. Electronic real-time assessment of patient-reported outcomes in routine care – first findings and experiences from the implementation in a comprehensive cancer center. *Support Care Cancer* 2016; **24**:3047–56.
- 15 Basch E, Deal AM, Dueck AC et al. Overall survival results of a trial assessing patient-reported outcomes for symptom monitoring during routine cancer treatment. *JAMA* 2017; **318**:197–8.
- 16 Big Data for Better Outcomes. Big data for better outcomes. Available at: <http://bd4bo.eu/index.php/big-data-for-better-outcomes> (last accessed 26 February 2018).
- 17 Grasser F, Beckert S, Kuster D et al. Therapy decision support based on recommender system methods. *J Healthc Eng* 2017; **2017**:8659460.
- 18 Tan SS, Gao G, Koch S. Big data and analytics in healthcare. *Methods Inf Med* 2015; **54**:546–7.
- 19 Schmitt J, Abraham S, Trautmann F et al. Usage and effectiveness of systemic treatments in adults with severe atopic eczema: first results of the German Atopic Eczema Registry TREATgermany. *J Dtsch Dermatol Ges* 2017; **15**:49–59.
- 20 Spuls PI, Gerbens LAA, Apfelbacher CJ et al. The International TREATment of ATopic Eczema (TREAT) Registry Taskforce: an initiative to harmonize data collection across national atopic eczema photo- and systemic therapy registries. *J Invest Dermatol* 2017; **137**:2014–16.