



Long-term disease control in atopic dermatitis using biologics



BSIP/UGC/Getty Images

Published Online
December 9, 2022

[https://doi.org/10.1016/S0140-6736\(22\)02347-9](https://doi.org/10.1016/S0140-6736(22)02347-9)

See [Articles](#) page 204

Atopic dermatitis is an inflammatory, itchy skin condition characterised by a fluctuating and chronic disease course. Effective therapies inhibit downstream immune signalling of interleukin (IL)-4, IL-13, IL-31,¹ and Janus kinase activity.² Biologics that target upstream cytokines, such as IL-1 α , IL-33, and thymic stromal lymphopoietin (TSLP), have so far been unsuccessful. OX40, a cell-surface glycoprotein, which is highly expressed on T cells and dendritic cells in lesional atopic dermatitis skin, works downstream of TSLP; OX40 stimulates proliferation and survival of activated T cells, some of which might become memory T cells.³

In *The Lancet*, Emma Guttman-Yassky and colleagues⁴ report the main findings from a multicentre, double-blind, placebo-controlled, phase 2b study of the anti-OX40 antibody rocatinlimab. The study was done at 65 sites in Canada, Germany, Japan, and the USA in 273 adults (109 [41%] women, 158 [59%] men; 171 (64%) Asian, 13 (5%) Black, 82 (31%) White, and one (<1%) other; mean age 37.9 years [SD 14.7] in the full analysis set of 267 patients) with moderate-to-severe atopic dermatitis. The primary efficacy endpoint was percent change from baseline to week 16 in the Eczema Area and Severity Index (EASI). After 18 weeks of treatment, EASI reductions were significantly higher in all patients treated with four different dosing regimens of rocatinlimab (rocatinlimab 150 mg every 4 weeks -48.3 [95% CI -62.2 to -34.0], $p=0.0003$; rocatinlimab 600 mg every 4 weeks -49.7 [-64.3 to -35.2], $p=0.0002$; rocatinlimab 300 mg every 2 weeks -61.1 [-75.2 to -47.0], $p<0.0001$; and rocatinlimab 600 mg every 2 weeks -57.4 [-71.3 to -43.4], $p<0.0001$) compared with patients who received placebo (-15.0 [95% CI -28.6 to -1.4]). 75% reductions in EASI (EASI-75) scores were reported in 44% of patients in the rocatinlimab 150 mg every 4 weeks group, 40% of patients in the rocatinlimab 150 mg every 4 weeks group, 54% of patients in the rocatinlimab 300 mg every 2 weeks group, 39% of patients in the rocatinlimab 600 mg every 2 weeks group, and 11% of patients in the placebo group. 90% reductions in EASI (EASI-90) scores were reported in 19% of patients in the rocatinlimab 150 mg every 4 weeks group, 12% of patients in the rocatinlimab 150 mg every 4 weeks group, 37% of patients in the rocatinlimab 300 mg every 2 weeks group, 19% of patients in the rocatinlimab 600 mg every

2 weeks group, and 4% of patients in the placebo group. The most common adverse events in the overall group of patients who received rocatinlimab and the placebo group were pyrexia (36 [17%] patients vs two [4%] patients), nasopharyngitis (30 [14%] patients vs nine [16%] patients), chills (24 [11%] patients vs no patients), headache (19 [9%] patients vs one [2%] patient), aphthous ulcers (15 [7%] patients vs no patients), and nausea (13 [6%] patients vs one [2%] patient). From weeks 18 to 36, patients in the four rocatinlimab groups continued to receive the same dose, whereas patients in the placebo group received rocatinlimab 600 mg every 2 weeks. After week 36, a 20-week off-treatment period was initiated. Of the patients who had an EASI-75 response at week 36, 73–96% across rocatinlimab groups maintained EASI-75 at week 56. During the off-treatment period, patients that received rescue treatment were kept in the study.

Although this study has limitations, such as predominately including Asian patients and allowing patients to stay in the study during the off-treatment period despite use of rescue treatment, the findings are important because they show that inhibition of midstream pathways, such as OX40, are effective and might lead to long-term disease control. 52-week data for lebrikizumab (IL-13 inhibiting biologic) showed that a high proportion of patients with atopic dermatitis maintained their EASI reductions when off systemic treatment after week 16.⁵ Data for dupilumab indicate resolution of atopic dermatitis in some patients,⁶ but there is no firm evidence of any of these medications being truly disease modifying. There is currently no data on the natural history of atopic dermatitis in adults,⁷ and it is impossible to verify whether patients had a natural improvement in atopic dermatitis severity (after effective treatment), as seen in the real world when medication use drops dramatically after flare resolution.⁸

To date, neutralising antibodies are not a concern in atopic dermatitis. Although some biologics per label can be dosed with longer treatment intervals than others (eg, the IL-13 inhibitor tralokinumab is given every 4 weeks in responders),⁹ off-label increased dosing intervals are also possible with dupilumab in patients with good disease control.¹⁰ In the study by Guttman-Yassky,⁴ two rocatinlimab regimens with 4-week application intervals

were investigated; the 600 mg rocatinlimab every 4 weeks regimen had a very good outcome. An evidence-based concept of increased dose intervals or treatment breaks of biologic therapy during times of complete or near complete disease control is needed in atopic dermatitis to limit unnecessary use of medication.¹¹ Data about when to reinstall biologic treatment following disease reactivation should be generated. Such an approach might be possible in a chronic, fluctuating disease, such as atopic dermatitis, because an increase in itch precedes atopic dermatitis activity and is therefore easy to detect. However, biologics for atopic dermatitis have slow onset of action; there is a risk that patients will not fully regain disease control and that rapid worsening of the slowly healing skin barrier will change the course of disease. Exit strategies for biologic treatments need to be carefully examined to advance their rapid development in atopic dermatitis.

JPT reports consulting fees from Coloplast; speaker's fees from Pfizer, AbbVie, Regeneron, Sanofi-Genzyme, LEO Pharma, Eli Lilly, and Almirall; and advisory board fees from Pfizer, AbbVie, Regeneron, Sanofi-Genzyme, LEO Pharma, Eli Lilly, Almirall, Arena Pharmaceuticals, Aslan Pharmaceuticals, and OM Pharma, all broadly related to atopic dermatitis. PS-G reports consulting fees from Coloplast; speaker's fees from Pfizer, AbbVie, Sanofi-Genzyme, LEO Pharma, Eli Lilly, Biomed, Almirall, L'Oreal, and Pierre Fabre; and advisory board fees from Pfizer, AbbVie, Regeneron, Sanofi-Genzyme, LEO Pharma, Galderma, and Eli Lilly, all broadly related to atopic dermatitis.

*Jacob P Thyssen, Peter Schmid-Grendelmeier
jacob.pontoppidan.thyssen@regionh.dk

Department of Dermatology, Bispebjerg Hospital, University of Copenhagen, Copenhagen DK-2400, Denmark (JPT); Department of Dermatology, University of Zürich, Zürich, Switzerland (JPT, PS-G); Christine Kühne Center for Allergy Research and Education, Davos, Switzerland (PS-G)

- 1 Ratchataswan T, Banzon TM, Thyssen JP, Weidinger S, Guttman-Yassky E, Phipatanakul W. Biologics for treatment of atopic dermatitis: current status and future prospect. *J Allergy Clin Immunol Pract* 2021; **9**: 1053–65.
- 2 Thyssen JP, Thomsen SF. Treatment of atopic dermatitis with biologics and Janus kinase inhibitors. *Lancet* 2021; **397**: 2126–28.
- 3 Elsnér JSH, Carlsson M, Stougaard JK, et al. The OX40 axis is associated with both systemic and local involvement in atopic dermatitis. *Acta Derm Venereol* 2020; **100**: adv00099–5.
- 4 Guttman-Yassky E, Simpson EL, Reich K, et al. An anti-OX40 antibody to treat moderate-to-severe atopic dermatitis: a multicentre, double-blind, placebo-controlled phase 2b study. *Lancet* 2022; published online Dec 9. [https://doi.org/10.1016/S0140-6736\(22\)02037-2](https://doi.org/10.1016/S0140-6736(22)02037-2).
- 5 Blauvelt A, Thyssen JP, Guttman-Yassky E, et al. Efficacy and safety of lebrikizumab in moderate-to-severe atopic dermatitis: 52-week results of two randomized, double-blinded, placebo-controlled phase 3 trials (ADvocate1 and ADvocate2). *European Academy of Dermatology and Venereology*; Milan, Italy; Sept 7–10, 2022 (abstr 3456).
- 6 Miyamoto S, Imai Y, Natsuaki M, Yamanishi K, Kanazawa N. Long-term remission of atopic dermatitis after discontinuation of dupilumab. *Acta Derm Venereol* 2022; **102**: adv00731.
- 7 Bieber T, Traidl-Hoffmann C, Schäppi G, Lauener R, Akdis C, Schmid-Grendelmeier P. Unraveling the complexity of atopic dermatitis: the CK-CARE approach toward precision medicine. *Allergy* 2020; **75**: 2936–38.
- 8 Egeberg A, Thyssen JP, Wu JJ, Pierce E, Terres JAR. Treatment patterns in Danish patients with atopic dermatitis before and after hospital referral. *Dermatol Ther* 2021; **11**: 499–512.
- 9 Blauvelt A, Langley RG, Lacour JP, et al. Long-term 2-year safety and efficacy of tralokinumab in adults with moderate-to-severe atopic dermatitis: interim analysis of the ECZTEND open-label extension trial. *J Am Acad Dermatol* 2022; **87**: 815–24.
- 10 Spekhorst LS, Bakker D, Drylewicz J, et al. Patient-centered dupilumab dosing regimen leads to successful dose reduction in persistently controlled atopic dermatitis. *Allergy* 2022; **77**: 3398–407.
- 11 Steinhart AH. Exit strategies for biologic therapy in IBD: is it too soon to stop? *Inflamm Bowel Dis* 2018; **24**: 669–70.

Machine learning to assess coronary artery disease status— is it helpful?



Over the past decade, massive, biologically rich datasets—and machine learning methods that can interrogate them—have allowed for the development of predictive cardiovascular disease diagnostics. These machine learning markers are designed to identify patients with undiagnosed disease or those at risk of future disease, often earlier and with better predictive accuracy than conventional guidelines.^{1–3}

The traditional approach to cardiovascular risk estimation has focused on a small set of variables that were assessed uniformly in prospective cohort derivation studies and easily ascertainable within clinical practice. For example, the US Pooled Cohort Equations estimate 10-year risk of developing atherosclerotic cardiovascular

disease among individuals aged 40–79 years on the basis of factors such as age, sex, race, smoking status, and total cholesterol.⁴ Although the utility of these scores has never been proven with a randomised controlled trial, practitioners routinely use them to guide decisions, such as whether to start a preventive medication. Alongside considerable advantages, such as ease of calculation and validation in carefully conducted cohort studies, these scores have several weaknesses. First, they are based on data from participants who enrolled decades ago, which might contribute to reports of miscalibration.⁵ Second, studied participants do not reflect the diversity of patients in practice—for example, none of the 24 626 participants studied were of south Asian

Published Online
December 20, 2022
[https://doi.org/10.1016/S0140-6736\(22\)02584-3](https://doi.org/10.1016/S0140-6736(22)02584-3)
See [Articles](#) page 215