and busyness level ($P = 0.03$), and positively associated with stress ($P < 0.001$) and air pressure ($P = 0.05$). In addition, POEM was significantly higher in weeks with high Birch ($P = 0.018$) and Elm pollen ($P = 0.008$). Daily temperature tended to associate negatively with POEM while daily active time and diurnal temperature range showed no association with POEM. POEM was higher in weeks with shorter sleep duration, however, not significant ($P = 0.061$). Occasionally, the associations between triggers and POEM indicated opposite responses in the study population (Fig. 2). iSCORAD was positively associated with the self-reported stress levels ($P = 0.002$) but not with any of the other passive data. iSCORAD was, however, strongly associated with POEM in a linear mixed effect model ($P < 0.001$). Our findings are in line with previous studies reporting that low humidity decreases skin barrier function and, for most subjects, increases AD symptoms[4] that discrepancies exist with regards to temperature, which may be both protective[3,4] and harmful,[7] and that AD symptoms can be triggered by a variety of pollens.[8,9] Furthermore, stress is a well-known trigger factor which this study also supports.[10] Overall, our data indicate that within AD, the importance of specific trigger factors varies from patient to patient. In conclusion, data collected passively through the smartphone (mainly GPS) is associated with patients' subjective disease severity (POEM). This was shown for air humidity and -pressure, pollen and overall busyness level supporting that lifestyle and environmental factors are linked to AD disease activity.

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The patients in this manuscript have given written informed consent to the publication of their case details.

Conflict of interest

Drs. Eiken, Laugesen, Isberg, Dutei, Deaconescu, Manole, Valk, Andersen and Zibert report personal fees (salary) from LEO Innovation Lab, part of LEO Pharma A/S, during the conduct of the study; Drs. Eiken, Laugesen, Isberg, Dutei, Deaconescu, Manole, Valk, Andersen and Zibert reports personal fees from (salary) Studies&Me A/S, owned by LEO Pharma A/S and personal fees (salary) from LEO Innovation Lab, part of LEO Pharma A/S, outside the submitted work during the last 36 months. Dr. Chiriac reports personal fees from LEO Pharma, outside the submitted work during the last 36 months. Drs. Thomsen and Ali have nothing to disclose.

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Dupilumab and conjunctivitis: a case series of twenty patients

Editor

In our Dermatology Unit, from May 2018 to January 2020, we enrolled 277 patients affected by moderate-severe forms of atopic dermatitis for the treatment with dupilumab. Six patients have been treated since about 104 weeks while eighteen patients since about 78 weeks. During the first examination, all patients gave written informed consent to the publication of their case details and received the prescription of trehalose/hyaluroate tear substitute to hydrate the conjunctival mucosa. The

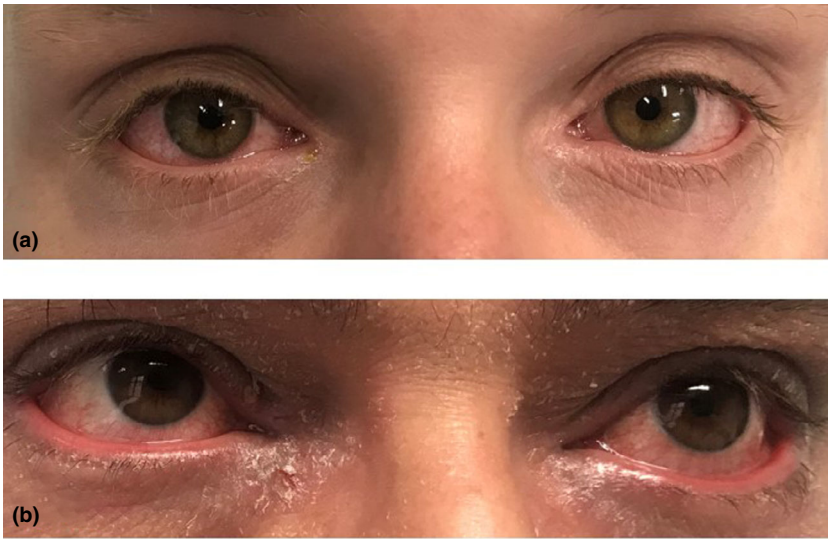

Figure 1 (a) Clinical image of non-specific, bilateral keratoconjunctivitis associated with dry eye, risen 8 months after the start of the treatment with dupilumab, in a 24-year-old male patient. (b) Bilateral keratoconjunctivitis associated with dry eye, enveloped 12 months after the start of the treatment with dupilumab, in a 54-year-old male patient.

ones with peripalpebral eczema were treated with tacrolimus 0.1% ointment. We indentified 20 cases of conjunctivitis (incidence: 7.2%). Interrogating patients, 6 of them admitted not to take preventive therapy (30% of the total with conjunctivitis). Excluding these, the incidence of conjunctivitis was equal to 5%. 19 patients were affected by a non-specific keratoconjunctivitis associated with dry eye (Fig. 1a-b), 1 patient presented a follicular conjunctivitis associated with limbitis (incidence of follicular conjunctivitis: 0.4%) (Fig. 2). Considering only the 14 patients affected by conjunctivitis that performed preventive therapy, history of previous conjunctivitis was found in 6 patients (42.8% of the total). The ocular involvement was monolateral in 11 subjects and bilateral in the remaining 3. Only two patients (0.7% of the total) interrupted therapy for non-responsive conjunctivitis (pre-existing the start of the biological drug and persisting after its cessation). The mean age of patients with conjunctivitis was 35 years (minimum age: 18; maximum age: 83), similar to the mean age of the total patients treated with dupilumab (36 years; minimum age: 18 years; maximum age: 83 years). Speaking about gender, 11 of 14 patients with conjunctivitis were male (78.5%), while in the total cohort 203 were male and 74 female. The mean EASI score of patients affected by conjunctivitis was equal to 37 (EASI range: 26–60), higher than the mean EASI score of the total 277 patients (equal to 28). All 14 patients had periparpebral eczema, 11 of them had seborrheic-like dermatitis and 11 facial eczema. Of 277 patients treated with dupilumab, 75 patients (27%) presented facial seborrheic-like dermatitis while 71 (26%) showed facial eczema without signs of seborrheic dermatitis. These patients were, respectively, treated with antifungal-corticosteroid cream, itraconazole tablets and tacrolimus 0.1% ointment. Considering the total of patients with facial eczema and peripalpebral eczema, (146 patients), the percentage of subjects who developed conjunctivitis is 9.5%. Conjunctivitis seems to be a tardive adverse effect: the mean time of onset from the start of therapy was sixth month of therapy (time lapse: 3–14 months), two patients showed the first episode after 12 months while a patient after 14 months. All subjects showed a remarkable improvement of their AD despite the conjunctivitis. All cases of conjunctivitis were treated with cortico-antibiotic in eye drops associated with tacrolimus ointment 0.1% with complete response in all cases except two. Cyclosporine in ophthalmic drops was prescribed in the patient with follicular conjunctivitis, with regression of the disease. Thanks to the prophylactic procedures, the incidence of conjunctivitis between

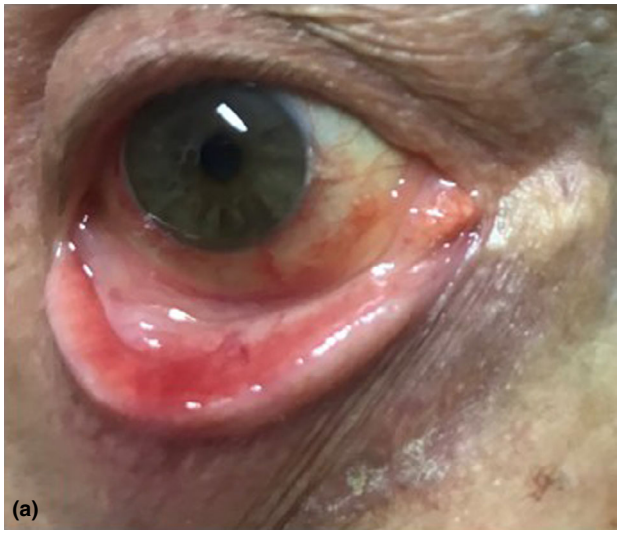

Figure 2 (a) Follicular conjunctivitis associated with limbitis confirmed by oftalmologist in a 83-year old male patient.

our patients was equal to 5%, lower than Phase III studies (incidence equal to 8%) and the real-life publications (incidence equal to 9–28%).[1-10] The incidence of conjunctivitis was higher considering patients with facial eczema (9.5%), despite specific therapy like antifungal-corticosteroid cream, tacrolimus 0.1% ointments and itraconazole tablets. A possible association between facial eczema and conjunctivitis is probable but more data are needed. Probably, prophylactic therapy, based on trehalose/hyaluroate tear substitute associated with the treatment for palpebral and facial eczema, reduced dry eyes and consequently conjunctivitis.

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A phase I clinical trial to evaluate the safety of HU-045 for treating moderate-to-severe glabellar lines: a pilot study

Dear Editor,

Recently, a new botulinum toxin type A (BoNTA), HU-045, was introduced by Huons Global Co., Ltd. (Seongnam, Korea). HU-045 is a *Clostridium* BoNTA (150 kDa) preparation comprising the same molecular components as the existing incobotulinumtoxinA. However, the efficacy and safety of HU-045 have not been explored. Accordingly, we performed a phase I clinical study to evaluate the safety and efficacy of HU-045 in the treatment of moderate-to-severe glabellar lines.

A 12-week prospective, single-arm, single-centre study, with 13 subjects presenting moderate-to-severe glabellar lines [facial wrinkle scale scores (FWS) of glabellar lines ≥2 at maximum glabellar frown], was performed (Fig. 1). At baseline, the glabellar line of each subject was treated with five intramuscular injections (0.1 mL; 4 U/0.1 mL), at a total of 20 U of HU-045.

The primary objective of this study was to evaluate the safety of HU-045 for 12 weeks after treatment. The incidence of treatment-emergent adverse events (TEAEs) was 23.08% (3/13). Adverse drug reactions (ADRs), serious AEs, serious ADRs and injection site reactions were absent. The reported TEAEs included 'dysmenorrhea', 'vaginal infection', 'hyperglycaemia' and 'glycosuria'. All TEAEs were determined to be 'not related' to the investigational drug. No symptoms such as headache, injection site pain and eye discomfort, which are frequent adverse reactions occurring after BoNTA injection into glabellar lines, were reported.[1–3] Additionally, it is known that the non-toxin proteins in the BoNTA complex can cause flu-like symptoms.[4] In this study, no such adverse reactions were observed. This may be because HU-045 is a 150-kDa preparation in which non-toxin proteins are removed and only effective neurotoxins are retained through purification processes. Based on the safety results, no specific irreversible adverse reactions were noted with the HU-045 strain, and excellent tolerability was achieved.

As the secondary objective of this study, the efficacy of HU-045 in the treatment of glabellar lines was evaluated in 12 out

