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RESEARCH ARTICLE

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UCOMB-real life data: treatment strategies for chronic urticaria patients with comorbidities

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ABSTRACT

Background: There is a lack of real-life safety data on treatment options for chronic urticaria in the presence of comedication and comorbidities.

Methods: We present a single-center UCARE pilot study of 212 outpatients with chronic urticaria. Patients were divided into three groups according to different CU therapies according to international guidelines.

Results: Of 212 patients, 108 (mean age 48.9 years, 71.3% female) had 59 comorbidities, including cardiovascular, autoimmune and malignant diseases. Patients were followed for a mean of 24.6 months (SD ± 21.3). Urticaria therapies were divided into three groups: A: 105 (97.2%) with omalizumab and 2nd generation antihistamines), B: 16 patients (14.8%): dual therapy with antihistamines and cyclosporine in 10 (9.3%), montelukast in five (4. 6%), dapsone in four (3.7%), hydroxychloroquine in one patient (0.9%), C: 12 (11.1%) patients received a third drug for 4.9 months (SD ± 3.2) and one quadruple therapy (2.1 months). 10 out of 12 (83.3%) patients received montelukast, two (16.7%) cyclosporine, two (16.7%) dapsone and one (8.3%) hydroxychloroquine as a third drug for chronic urticaria.

Conclusions: Combining treatment modalities for chronic urticaria and comorbidities are available and feasible with a good safety profile.

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KEYWORDS
Chronic spontaneous urticaria; wheals; angioedema; systemic therapy; comedication; comorbidity; real-life

1. Introduction

Chronic urticaria (CU) afflicts a significant portion of the world population, with a lifetime prevalence of 1.4%, resulting in negative impacts on patients' quality of life (1,2).

The primary treatment for CU is a second-generation antihistamine (sgAH) administered at dosages up to four-fold. If signs and symptoms continue to recur, add-on treatment with omalizumab (OMA), an anti-IgE antibody, should be considered (3). OMA is effective and mostly well-tolerated by patients (4). However, some CU patients do not benefit from OMA and need more effective therapy (5–7). Moreover, CU is connected with coexisting conditions like atopic dermatitis, autoimmune and cardiovascular disorders, and psychological disorders, as well as sleep disturbances, which, in many cases, necessitate medication (8–10). However, data on the safety of combined therapeutic approaches and long-term treatment for CU in such cases is limited (11).

2. Materials and methods

Retrospective analyses were performed at the Urticaria Center of Reference and Excellence (UCARE) of the Department of Dermatology and Allergy at the University Medical Center in Mainz, Germany. The data was collected using a questionnaire created by UCARE members of UCARE Centers, who have coauthored this manuscript. Overall, 212 CU outpatients were examined for the following inclusion criteria: treatment with a higher than standard-dosed antihistamine and receiving at least one more systemic drug with at least one comorbidity and comedication or receiving a triple therapy (TT). Demographic data and treatment plans were documented. A special questionnaire, developed by experts, was used for this purpose. The assessment of side effects was based on patient reports documented during patient visits. Different treatment strategies were compared: Group A = Double treatment (DT): sgAH and OMA; Group B = sgAH combined with another therapeutic agent different

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from OMA; Group C = Triple therapy (TT) with a sgAH, OMA and another drug, or quadruple therapy (QT) consisting of a sgAH, OMA, montelukast, and hydroxychloroquine.

The aim of this investigation was to assess the treatments recommended for CU by the international guideline in a real-life setting. Specifically, we assessed if the recommended treatments are suitable for CU patients with comorbidities and/or comedications in a real life settings.

Mobility exists within groups A, B and C. Patients in whom, for example, DT consisting of OMA and sgAH was not sufficient can also appear in group B after changing the second CU drug and/or in group C after adding a third drug.

2.1. Results

Of 212 patients with CU, 108 (50.9%) fulfilled the inclusion criteria. In the other 104 patients no comorbidity was recorded and/or no DT (no up-dosed sgAH and/or no second systemic treatment) was used. The mean age of the included patients was 48.9 years (SD ± 15.0), ranging from 14.1 to 78.5 years. The average duration of CU until therapy initiation was 4.6 years (SD ± 5.6). Most patients were female (77 of 108, 71.3%), and 67 (62.0%) and 38 (62.0%) patients had standalone CSU and CSU combined with CIndU, respectively. Three patients (2.8%) had mast cell mediator-associated angioedema (AE) without wheals (Table 1).

Group A: 105 of 108 (97.2%) patients received standard therapy with up-dosed sgAH and OMA. Three of 108 (2.8%) were in group B or C. Of these, 104 (99.0%) patients had at least one comorbidity and 100 (95.2%) had at least one co-medication, in addition to their CU therapy with a sgAH and OMA and sgAH)

Group B: 16 of 108 (14.8%) patients were treated by different CU therapies. Due to the fact, that patients were non-responders in Group A, they were treated with sgAH and instead omalizumab they received in 10 patients (9.3%) cyclosporine, in five patients (4.6%) montelukast, in four patients (3.7%) dapsone, and in one patient hydroxychloroquine. 13 of 16 (81.3%) had at least one comorbidity and 12 of 16 (75.0%) at least one co-medication alongside the different combinations mentioned above (Supplement Figure S1).

The mean duration for a DT in either group A or B was 24.6 months (SD ± 21.3).

Group C: A total of 12 of 108 patients (11.1%) received additional to sgAH and OMA a third therapeutic agent for a mean duration of 4.9 months (SD ± 3.2). 10 of these 12 patients (83.3%), received montelukast, two patients (16.7%) cyclosporine, two patients (16.7%) dapsone and one patient (8.3%) hydroxychloroquine.

In seven out of 12 patients (58.3%) who received TT, comorbidities were present. In five out of 12 (41.6%) co-medication was given (Supplement Figure S2).

In one case a QT consisting of sgAH, OMA, montelukast, and hydroxychloroquine was necessary for 2.1 months.

The number of therapies exceeds the number of patients, because in some cases therapeutic strategies were changed for the same patient.

Table 1. Patient demographics.

Patient characteristic	
Age, in years, mean ± SD	48.9 ± 15.0
Gender	
Female, n (%)	77 (71.3%)
Male, n (%)	31 (28.7%)
Urticaria type	
Standalone CSU, n (%)	67 (62.0 %)
CSU & CIndU, n (%)	38 (35.2%)
Isolated AE, n (%)	3 (2.8%)
Duration of dual therapy for CU in months, mean ± SD	24.6 ± 21.3
Duration of triple therapy for CU in months, mean ± SD	4.9 ± 3.2

CSU = chronic spontaneous urticaria, CIndU = chronic inducible urticaria, AE = angioedema; *n* = 108.

2.2. CU therapy in the presence of comorbidities

Our 108 CU patients with comorbidities had 59 distinct coexisting conditions, most commonly hypothyroidism, hypertension and atopic diseases (Table 2). Common co-medications included L-thyroxine (41.7%), beta-blockers (18.5%), AT-1 receptor antagonists (13.9%), antiplatelet drugs (10.2%), statins (7.4%) and selective

Table 2. Comorbidities of patients.

	n	%
Comorbidity		
Hypothyroidism	50	46,3%
Hypertension	47	43,5%
Atopies	**27**	25,0%
Allergic rhinoconjunctivitis	21	19,4%
Allergic bronchial asthma	10	9,3%
Atopic dermatitis	3	2,8%
Depression	16	14,8%
Sleep disorders	14	13,0%
Dyslipidemia	12	11,1%
Diabetes I and II	12	11,1%
Allergies	12	11,1%
Autoimmune diseases	**12**	11,1%
Psoriasis	3	2,8%
Ulcerative colitis	2	1,9%
Lupus erythematosus	2	1,9%
Celiac	2	1,9%
Crohn's disease	1	0,9%
Myasthenia gravis	1	0,9%
Vitiligo	1	0,9%
Subacute cutaneous lupus erythematosus	1	0,9%
Bechterew's disease	1	0,9%
Family Mediterranean fever	1	0,9%
Chronic pain	9	8,3%
Coronary artery disease	5	4,6%
Malignancies	**4**	3,7%
Active breast cancer	1	0,9%
State after breast cancer	1	0,9%
Chronic lymphatic leukemia	1	0,9%
Myeloproliferative Syndrome	1	0,9%
Cardiac arrhythmia	4	3,7%
Chronic gastritis	4	3,7%
COPD	4	3,7%
Restless legs-syndrome	3	2,8%
Hyperuricemia	3	2,8%
Iron deficiency	3	2,8%
Anxiety disorder	3	2,8%
Sleep apnea	3	2,8%
Benign prostatic hyperplasia	2	1,9%
Migraine	2	1,9%
Factor- V- Leiden mutation	2	1,9%
Hepatitis C	1	0,9%
Chronic hepatitis B	1	0,9%
Peripheral arterial occlusive disease	1	0,9%
von-Willebrand-syndrome	1	0,9%
Osteoporosis	1	0,9%
Kallmann-syndrome	1	0,9%
Bladder hyperactivity	1	0,9%
Hypoparathyroidism	1	0,9%
Adrenocortical insufficiency	1	0,9%
Thalassemia minor	1	0,9%
Eosinophilic esophagitis	1	0,9%
Endometriosis	1	0,9%
Onychomycosis	1	0,9%
Polycystic ovary syndrome	1	0,9%
Diverticulosis	1	0,9%
Chronic diverticulitis	1	0,9%
Fructose intolerance	1	0,9%
Protein S-deficiency	1	0,9%
Vitamin D-deficiency	1	0,9%
Acid reflux	1	0,9%
Herpes labialis	1	0,9%
Chronic Bronchitis	1	0,9%
Hyperthyroidism	1	0,9%

Table 3. Duration of co-medication of the most frequent comorbidities.

Co-medication	Mean of co-medication duration ± SD next to DT for CU in months, *median*	95% confidence interval Mean
Co-medication of thyroid dysfunction	22.1 ± 18.5, *16.9*	17.0–27.1
Co-medication of hypertension	26.4 ± 23.2, *21.4*	20.0–32.8
Co-medication of cardiovascular prophylaxis	25.5 ± 23.8, *15.6*	12.8–38.2
Co-medication of dyslipidaemia	17.2 ± 20.1, *7.7*	6.1–28.3
Co-medication of diabetes	19.0 ± 22.6, *9.0*	5.9–32.0
Co-medication of depression	16.2 ± 15.7, *11.3*	9.4–22.9
Co-medication of sleep disorders	6.4 ± 6.8, *3.8*	1.2–11.7

serotonin reuptake inhibitors (5.6%). Supplementary Table 1a, 1b and 1c illustrates the distribution of comedication combinations for comorbidity in conjunction with various forms of CSU treatment. When comorbidities such as malignancies, chronic inflammatory diseases, and hepatitis C are present, the duration of comedications is carefully monitored and described in detail. Tables 2 and 3 provide additional specific information.

Thyroid disorders were observed in 50 out of 108 patients (46.3%). Of the 50 patients, 49 (98.0%) were from group A, while 6 (12.0%) and 4 (8.0%) were from groups B and C, respectively. Among the 50 patients, 18 (36.0%) reported a diagnosis of Hashimoto's thyroiditis (HT).

2.2.1. Metabolic syndrome/disorders/cardiovascular comorbidity

Of the 108 patients observed, 47 suffered from arterial hypertension, representing 43.5% of the sample. In group A, 45 of 47 patients (95.8%) had arterial hypertension, while in group B and group C, the numbers were 6 of 47 (12.8%) and 2 of 47 (4.3%), respectively. 15 patients receiving cardiovascular prophylactic treatment belonged to group A, with only one of these patients (6.7%) also belonging to group B. Of the total sample, 15 patients (13.9%) received cardiovascular prophylaxis. Furthermore, 4 of the patients (26.7%) who were given prophylaxis had coronary artery disease. Out of 108 patients, 12 (11.1%) had dyslipidaemia, with all cases occurring in group A and three of the 12 (25.0%) also presenting In group B. Among the group, 11 (10.2%) patients were identified as suffering from diabetes mellitus type II, while one patient (0.9%) had diabetes mellitus type I. Moreover, 12 of the diabetes mellitus patients were in group A, with two found to be in group B as well.

2.2.2. Depression

Out of the 108 patients, 16 (14.8%) experienced depression alongside chronic spontaneous urticaria. All 16 of these patients belonged to group A, with two out of the 16 (12.5%) belonging to group B, and one out of the 16 (6.25%) belonging to group C. Due to this comorbidity, the only decision taken was to discontinue one treatment, as a preventive measure. The therapy in this patient involving sgAH was stopped due to depression but OMA was continued.

2.2.3. Sleep disorders

14 of 108 (13.0%) patients reported sleep disturbances. 13 in group A and one of 108 (0.9%) in group B.

2.2.4. Malignancies

In Group A, four out of 108 patients (3.7%) disclosed malignancies prior to or during treatment for CU. Amongst those patients, two suffered from breast cancer and received anti-cancer therapy: epirubicin and cyclophosphamide (19.6 m), and in the second case, anastrozole (14.3 m) was prescribed. One patient with myeloproliferative syndrome was treated with an antiplatelet agent (56.4 m). One patient with chronic lymphatic leukemia did not receive any co-medication.

2.2.5. Chronic inflammatory diseases

One patient, comprising 0.9% of the total of 108, in Group A required systemic treatment for atopic dermatitis, leaving to parallel use of dupilumab with DT. This combination lasted for 4.4 months. OMA was discontinued after CU control.

2.2.6. Chronic infections

One patient in Group A, comprising 108 individuals (0.9%), exhibited hepatitis C symptoms whilst being treated with anti-viral drugs sofosbuvir and ledipasvir for 5.2 months, alongside DT. However, complete remission of the condition transpired.

2.3. Side effects to CU medication and adverse events

In general, 80 of 108 patients (74.1%) reported adverse events and/or side effects during the monitored period. 42 of 108 patients (38.9%) reported side effects due to CU therapy. 36 of 105 (34.2%) patients in group A, 8 of 16 (50.0%) patients in group B and one of 12 (8.3%) patient in group C (Supplement Tables 2 and 3). It should be noted that there were no significant side effects that led to the discontinuation of CU medication, unless otherwise specified.

The most frequent side effects were related to sgAH in 28 patients (25.9%), 27 in Group A and one in Group B mentioning adverse events like fatigue in 20 of 28 (71.4%), headache, abdominal pain and weight gain (7.1%). In 18 of 28 patients these side effects subsided or disappeared after changing to another sgAH, combination therapy for CU with sgAH and OMA was continued.

In 12 out of 105 patients in group A (11.4%), the following side effects associated with OMA were observed: Therapy stopped in one case due to muscle, joint pain, and fatigue after a single OMA injection. Dapsone and sgAH were used for treatment instead. In another patient, uncertified angina pectoris symptoms occurred shortly after OMA injection, but no pathology was found. 12 (11.4%) patients reported the following side effects after OMA: Headache and fatigue were reported by seven patients each (6.7%), while heat sensation, nausea, and muscle and joint pain were observed in a single case each. One patient (0.9%) experienced idiopathic facial paralysis one day after receiving the OMA injection, although a direct correlation was ruled out. In 10 of the 12 cases, treatment could be sustained.

Overall, in Group B, 10 out of 16 patients (62.5%) were administered dual therapy for CU, comprising CsA and sgAH. Furthermore, two more patients were given CsA as part of a triple therapy in Group C. Out of the CsA patients, 8 (66.7%) reported side effects. Side effects reported include gastrointestinal problems in three patients (25.0%), gingival hyperplasia, hypertrichosis and hypertension in two patients (16.7%), as well as sensory disturbances, weight gain, fatigue, creatinine increase, headache, dizziness and gingival bleeding in a single patient (8.3%). There was also one undefined anaphylactoid reaction in DT, which resulted in immediate discontinuation of CsA. Due to safety concerns, six out of ten patients (60.0%) were discontinued and switched. The average duration of DT treatment with CsA was 5.3 ± 6.2 months.

Six out of 16 patients (37.5%) in group B were administered dapsone for CU. Among these, four out of six patients (66.7%) received dapsone in combination with sgAH as part of DT, while the remaining two (33.3%) received it as part of TT. Two cases (33.3%) reported side effects, with one patient experiencing occasional shortness of breath and the other developing methemoglobinemia, which led to discontinuation of therapy and subsequent switching to OMA and sgAH. No anemia was associated in these cases.

Two out of the 16 (12.5%) patients in Group B were administered hydroxychloroquine. One patient received a combination of hydroxychloroquine with sgAH, while the other was given hydroxychloroquine as part of TT. However, the treatment with hydroxychloroquine for the latter was halted due to visual impairment. Five out of 16 (31.3%) patients received montelukast as part of DT for Group B. In Group C, montelukast was used as the third component of TT for 10 out of 12 patients (83.3%). There were no reports of side effects due to the use of montelukast.

3. Discussion

Chronic spontaneous urticaria is an inflammatory systemic disease with a high burden of disease and high prevalence of comorbidities (8–10). Within our cohort of 108 CU patients with comorbidities, we identified 59 distinct comorbidities.

Although the gold standard therapeutic option for CSU is OMA combined with up-dosed sgAH (12,13) at least approximately 10–15% of patients with CSU, remain insufficiently treated (5–7). This is in line with our data: 12 out of 108 patients (11.1%), received TT because of insufficient treatment. Limited information is available regarding the successful use of sgAH with OMA and a third therapy, such as CsA (14). One study describes the use of immune suppressants (CsA in 16 patients, MTX and azathioprine in one patient each) in combination with high-dose OMA, for 14 months (SD ± 8) as safe. In our study, the duration of DT with CsA was 5.3 months (SD ± 6.2), which is consistent with the data obtained from another trial, where 72.7% of patients on CsA experienced side effects at two months and 64.5% at four months of therapy (15). Two studies with a limited number of patients, describe the use of OMA alongside with CsA or MTX as safe in the majority of patients ($n=15$ and $n=21$) (6,14) However, in our cohort six of 12 (50,0%) therapies with CsA were discontinued due to side effects.

Another study described three cases where dapsone and colchicine were safely added to the sgAH and OMA therapy regimen (16). In our cohort, two cases received dapsone in addition to sgAH and OMA (one case of TT with comorbidities and co-medication and one case colchicine for familial Mediterranean fever).

The findings of this study demonstrate that DT is a safe treatment option for CU/CSU patients with comorbidities or co-medication, even when used in combination with other therapeutic agents. With the exception of one case, DT treatment did not require complete discontinuation due to comorbidity, medication, or concomitant therapy. In one instance, OMA was discontinued as a result of suspected side effects. In addition to being able to use a third drug for CU (TT) for a duration of 4.9 months (SD ± 3.2) without interference, it is noteworthy that seven out of 108 patients (6.4%) had comorbidities and co-medications along with TT (Supplement Figure S1). Side effects under OMA were reported by 11.4% of patients who were undergoing OMA and sgAH treatment. Only one case resulted in OMA being discontinued due to suspected side effects. Similarly, in the OMA phase III trial, 11% of patients reported experiencing at least one adverse reaction with identical side effects to those in our cohort (17). Consequently, our real-life data indicate that the frequency of side effects of OMA in a patient population with comorbidities and co-medication is similar, with an average treatment period of 27.7 months.

3.1. Comorbidities with Co-medication and CU

In order to place the prevalence of the comorbidities in the epidemiological context of CU we refer to the total of 212 patients with CU.

In our cohort four of 212 patients (1.9%) with CU had malignancies, two breast-cancer, two haemato-oncological. Therapy consisted of epirubicine/cyclophosphamide respectively anastrozole as chemotherapy as well as an antiplatelet agent. There were no limitations in regard of cancer or cancer therapy during the time of observation, which is of great importance as there are only few published data regarding the effects of OMA on malignant diseases or impaired efficacy of OMA in cancer treatment (18,19). In case of cancer and its treatment, a CU therapy consisting of sgAH and OMA was safe, possible and feasible given a close monitoring.

In 12 of 212 patients (5.7%) autoimmune diseases other than Hashimoto's thyroiditis and type I diabetes mellitus were reported, i.e. psoriasis, ulcerative colitis, systemic lupus erythematosus(SLE), celiac disease, Crohn's disease, myasthenia gravis, vitiligo, subacute cutaneous lupus erythematosus(SCLE), Bechterews disease and familial Mediterranean fever. The prevalence of ulcerative colitis in CSU patients is described as 0.9%, which is in concordance with our data. For vitiligo (0.9%), our proportion differs by 0.1%. The proportions for celiac disease (1.9%), SLE (1.9%) and psoriasis (2.8%) are comparable (20). OMA was paused precautionary for six months in one case of SLE due to an episodic disease flare with vasculitic complaints and chilblain-like symptomatology. However, there was no sign of OMA being the cause. If there is a need to proceed or initiate CU therapy in patients with chronic inflammatory diseases, our data shows that a concomitant (co)-medication despite the intake of sgAH and OMA is safe and possible.

The percentage of thyroid dysfunction is reported as 0–42.6% (clinical) and 0–31% (subclinical), the proportion of Hashimoto Thyroiditis (HT) as 0.5–27.5% (21). The proportion without differentiation between clinical and subclinical SD dysfunction in our cohort is 23.6%, with 8.5% for HT. Simultaneous co-medication was possible in group A, B and C.

Hypertension is a prevalent comorbidity in CU, with a prevalence ranging from 18.1% to 41.3% (11,22–25). This is consistent with our research, indicating a hypertension prevalence of 22.2%. Furthermore, DM type II was found to be prevalent in 5.2%, in keeping with the findings of two recent studies (5.2% or 13.9% respectively) (23,24). Regarding dyslipidaemia, values of 22% and 41.6% can be found in the literature (11,23), our rate of 5.7% is far below this. Our findings indicate a possible underreporting, despite regular assessment of comedication changes. Based on our data and the available literature, the estimated prevalence of coronary artery disease (CAD) in patients with urticaria ranges from approximately 1.7% to 1.9% (24).

The prevalence of CAD in our patient group is lower compared to the worldwide average of 5–8% (26). This could be attributed to the younger age of our patients, which is comparable to other studies on CSU or CU. A DT for CU is safe and possible in patients with existing cardiovascular comorbidity/co-medication.

Anxiety disorders are present in 30% and depression in 17% of patients with CSU (27). In our current evaluation, depression

represented 7.5%, sleep disorders 6.6% and anxiety disorders 1.4% of the population. The prevalence is significantly lower compared to literature, which also could be partially explained by underreporting. This implicates, that physicians need to actively ask about mental health symptoms (3). 13 out of 16 patients safely received pharmacological treatment for depression, however a possible effect of sgAH therapy was closely monitored and led to a precautionary discontinuation in one case.

The medication with the most side effects was sgAH ($n = 28$) (25.9%). In 18 of the 108 patients (16.7%), the sgAH was changed to another. However, considering the treatment length (24.6 months; SD ± 21.3) with regular follow-up visits, may alone increases the probability of several symptoms being interpreted as side effects. The most common reported symptom was fatigue in 20 (18.5%) patients. The sgAHs used were: rupatadine, fexofenadine, loratadine, desloratadine, bilastine, cetirizine, levocetirizine and ebastine.

Dapsone, a second-line treatment option, was administered to six patients within our cohort. Co-administration of both montelukast and dapsone, as a third therapeutic agent, did not entail any risk to DT. Hydroxychloroquine was administered to two patients, even as part of a QT (sgAH, OMA, montelukast and hydroxychloroquine). One patient had to stop therapy after 4.7 months due to a decline in visual acuity. Apart from this, TT or escalation thereof was feasible and safe, and DT remained uncompromised. Patients receiving dapsone for CU presented a range of comorbidities, including diabetes, hypertension, hypercholesterolemia, hypothyroidism, chronic gastritis, sleep disorders, adrenal insufficiency, and Factor V-Leiden Syndrome. Dapsone has a confirmed track record as a medication for various other autoimmune/autoinflammatory diseases.

3.2. Strengths and limitations

Our data are summarized based on the physician's documentation during each visit in average every 3 months and patient's history only. However, by embedding our data in the context of previous literature, the validity of our registered prevalence becomes evident. The strength of this observation is the exact documentation of duration of urticaria medication as well as co-medications and comorbidities, suggesting the safety in both patient groups. Furthermore, this study offers essential real-world data concerning the occurrence of comorbidities in CU patients that can only be obtained in a real-life environment, especially in patients not responding adequately to standard treatment where no approved treatment is available for now. These findings lend support to physicians in their daily practice for optimal CU patient treatment. However, additional data is needed to reinforce these discoveries, for example, through multi-center non-interventional studies or registries. Consequently, an international UCARE-project is currently being prepared worldwide.

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Disclosure statement

Petra Staubach: Has served as a consultant, in clinical studies and/or speaker to AbbVie, Almirall-Hermal, Amgen, Beiersdorf, Biocryst, BMS, Boehringer-Ingelheim, CSL-Behring, Eli-Lilly, Galderma, Hexal, Janssen, Kalvista, LEO-Pharma, L'Oreal, Novartis, Octapharma, Pfizer, Pflüger, Regeneron, Shire, Takeda, Regeneron, Sanofi-Genzyme und UCB Pharma. She has no conflicts of interest related to the content of this article.

Benedikt Bilo: nothing to declare.

Caroline Mann: worked in clinical studies of Novartis and Sanofi, received travel supports/grants/invited speaker by Almirall, Novartis, L'Oreal, Pfizer and Sanofi.

Joachim Fluhr: Has served as a consultant and/or speaker to Bayer, B. Braun, Beiersdorf, Bioderma, Expanscience, Leo, Nestlé Skin Health, Neo Pharma, Pierre Fabre, Roche-Posay, Sebapharma, Unilever, Coloplast, Galderma, Mann & Schröder, Medicorum TAM, Courage& Khazaka, ECARF, Lilly, NAOS. He has no conflicts of interest related to the content of this article.

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