

Contact allergy to topical corticosteroids – results from the IVDK and epidemiological risk assessment

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Summary

Background: Contact allergy (CA) to topical corticosteroids (CS) is relatively rare; however, current data from Germany are not available. Furthermore, valid risk assessment needs to take into account of the actual exposure to CS in the population.

Patients and Methods: The reaction profile of 9 CS included in a “CS test battery” of the German Contact Dermatitis Research Group (DKG) in patients seen in German clinics belonging to the Information Network of Departments of Dermatology (IVDK; www.ivdk.org) between 01/1995 and 12/2004 was analyzed. Applying the “Clinical Epidemiology/Drug Utilization Research” approach, annual incidences of CA to CS in Germany were extrapolated. These estimates were used as numerator for a relative incidence (RI) estimate which used exposure in terms of “defined daily doses” (DDD) to the respective CS as denominator, the latter information collected by the AOK Research Institute (WIdO).

Results: On average, 7.4 % of all patients were patch tested with the CS series, mostly yielding < 1 % positive reactions. Exceptions included hydrocortisone 17-butyrate (1.5 %), amcinonide (1.6 %) and budesonide (2.6 %). With a RI of 10.7, 23.6 and 4.9 per 100 000 DDD, respectively, the three CS mentioned classify as moderate topical drug allergens. Clobetasol 17-propionate and triamcinolone acetonide both yielded a RI of 1.4/100 000 DDD, indicating low sensitization risk. For hydrocortisone, betamethasone, prednisolone and dexamethasone (RI < 1/100 000 DDD) the risk of sensitization appears minute.

Conclusions: The results support and extend previous evidence on the CA risk of CS, adding to a therapeutic index and risk assessment.

Introduction

Contact allergies (CA, used here synonymously with the term contact sensitization) to topical corticosteroids (CS) have been known for several decades (reviews e. g. [1–3]). As European data seem to indicate that CA to CS are relatively

frequent among patch test patients (0.9 to 4.4 % positive reactions to tixocortol pivalate, 1 to 1.5 % to budesonide in consecutively tested patients), it was recommended to include these two compounds as screening allergens in the European standard series [4]. Such high

sensitization prevalences have not been identified in consecutively tested patients in Germany or Australia; furthermore the clinical relevance of positive test reactions often remains unclear [5, 6]. Thus, the German Contact Allergy Group (Deutsche Kontaktallergie-Gruppe, DKG)

of the German Society of Dermatology (Deutsche Dermatologische Gesellschaft, DDG) did not follow the European recommendation. A diagnostic dilemma does exist for CA to CS: CS are often employed in the treatment of various forms of dermatitis; an apparent deterioration during therapy is often interpreted as treatment failure but not as secondary CA to CS. In addition, the appropriate patch testing methods (concentration, vehicle, reading time frame) are unclear.

Since 1991 the DKG has used a uniform CS test battery; the first results for 1388 patients have been published [7]. The battery in the form presented here has been used since 2001 only, which is why the test numbers for the last three allergens are lower. The present analysis not only presents the profile of observed (cross-) reactions to the 9 CS in this test battery, but also assesses the frequency of CA on a population level. This is related to exposure in order to obtain a more valid quantification of the CA risk of the individual substances than would be possible by exclusively considering clinical data.

Methods

Clinical contact allergy data

Since 1989 the Information Network of Departments of Dermatology (IVDK, www.ivdk.org) exists as a cooperation originally of 8 and at present of 45 clinics in Germany, Austria and Switzerland. Participants in the IVDK, who are all members of the DKG, use special software ("WinAlldat/IVDK") to document standardized history data and patch test results [8] which are then transmitted in anonymous form to the IVDK main office in Göttingen. The continual surveillance of contact allergy frequency by the IVDK has the goal of identifying increasing trends in the frequency of individual contact allergens or marked increases of specific CA in specific subgroups in order to make early interventions possible [9]. Only data meeting the quality criteria of the IVDK [10] enter into pooled analyses such as the present. The descriptive and analytic epidemiologic analyses using SAS software (version 9, SAS Institute, Cary, NC) were done in accordance with the respective guidelines [11]. To quantify the concordance of positive (vs. non-positive) test reactions in terms of "agreement in excess of

chance" the respective standard measure of Cohen's kappa coefficient with the associated asymptotic 95 % confidence interval (CI) is used [12].

The present analysis is based on the data of 6240 of a total of 87 224 patients (7.4 %) patch tested between January 1995 and December 2004 in the German IVDK clinics that had the "corticosteroid battery" applied in a targeted manner. The limitation to German clinics was necessary because extrapolation to the population level has up to now only been established for Germany, but not for Switzerland and Austria (see below) and further the standardized prescription data of the WIdO Research Institute, Bonn, apply only for the Federal Republic of Germany (see below).

"CE-DUR" extrapolation to the general population

"Clinical Epidemiology and Drug Utilization Research" (CE-DUR) is an approach where clinical-epidemiologic data (the patch test results from patients) are combined with pharmaco-epidemiologic methods (drug utilization research). Concretely, this includes the following steps [13]:

1. The annual sales numbers of the patch test standard series, which is applied to (almost) each patient with suspected contact allergy and which is not used for any other purpose, is obtained from the manufacturers represented in Germany (Hermal, Reinbek, Germany; HAL/Brial, Greven, Germany; Chemotechnique, Malmö, Sweden; Mekos Lab., Hillerød, Denmark).
2. The cumulated annual sales numbers of all manufacturers yield a raw number of annual patch tests in Germany under the assumption of 100 tests per 10 ml allergen preparation.
3. A series of correction factors following three scenarios ("conservative", "medium" and "extreme" estimate) are used with this crude number. Considered are (a) the proportion of unused "expired" test material, (b) the proportion of those already previously tested, so that only first tests are evaluated and (c) the fact that a relatively small proportion of persons with probable contact allergy consult a dermatologist for testing.

4. In the case of testing with a special test battery as here, it is also assumed that the proportion of patients exposed to this test battery in the IVDK is representative for Germany.

The thus calculated numbers in the present case, in the three scenarios, yield the annual number of patients eligible for patch testing in Germany with the CS battery due to suspected allergic contact dermatitis caused by CS. By multiplication with the respective probability of an allergic test reaction estimated by the observed CA prevalences in the IVDK the probable annual number, again in three scenarios, of newly diagnosed sensitizations to the respective substance is obtained, which is averaged over a 10-year time period.

Prescription data of WIdO

Since 1985 the Drug Prescription Report (Arzneiverordnungs-Report) has analyzed the drug prescriptions of the statutory health insurance (Gesetzliche Krankenversicherung, GKV) (e. g. for the last year of the study time period [14]). The analyses are based on the data of the research project GKV drug index in the AOK Research Institute (WIdO, Bonn, Germany) and include all prescriptions reimbursed by the statutory health insurance and dispensed in public pharmacies within one calendar year. Not included are prescriptions reimbursed by private health insurances, dispensed in hospitals as well as drugs that are purchased privately without prescription in pharmacies (OTC business). For documentation the anatomic-therapeutic-chemical (ATC) classification of the World Health Organization (WHO) is utilized, which has been expanded by WIdO for the specific requirements of the German market [15]. For the assignment of the respective prescribed amount according to defined daily doses (DDD) to the selected active ingredients, the ATC code is used for mono-preparations. For combined preparations, such as CS with topical antibiotic, in addition to the ingredients covered by ATC, further ingredients are also considered to achieve complete coverage of CS exposure. The DDD is an instrument of measurement for drug utilization and by definition is the assumed mean daily maintenance dose for the main indication of a drug for adults. A detailed description of the methods of the ATC

classification and determination of DDD for the German drug market can be found in Fricke et al. [15]. For topical preparations the amount applied at each use is estimated with the help of standard doses ("unit dose"), which is 1 g (of the topical preparation). When no specific DDD exists for the active ingredient, the DDD is calculated as the product of the "unit dose", i.e., 1 g, and the application frequency per day.

For the present analysis the WiDO supplied prescription data in the form of DDD for preparations intended for use on the skin or adjacent mucous membranes, classified according to ATC and collected at the level of the active ingredient. It deserves special mention that not only the DDD of directly identifiable mono- or combined preparations that contained a particular agent as (main) ingredient were identified, but also combined preparations containing an ingredient not identifiable by ATC. For this all possible ATC codes, in which such ingredients could be included, were linked to the respective registered products in the WiDO data bank and then researched on the level of the preparations if a respective ingredient was present for which an annual DDD of this ingredient associated with this preparation could be determined and assigned to it. Of the CS examined in the study time period only hydrocortisone was not exclusively available by prescription but in a concentration of $\leq 0.25\%$ also available "over the counter" (OTC), resulting in an underestimation of exposure when only the prescription data for this active agent are considered.

Using the annual incidence of CA towards the individual active agents estimated by CE-DUR as numerator and the exposure "person time under risk" measured in DDD as denominator, in the three scenarios the "relative incidence" of CA was calculated; for further details on methods as well as on calculation of the interval estimate (CI) of RI see Menezes de Pádua et al. [16] and [17].

Results

The CS test battery was applied to 7.4 % of patients tested. The reaction profile of the nine CS is depicted in Table 1. Deviations (to lower numbers) from the total test number result from temporary non-availability of allergens, not testing in individual cases or

changes in the composition of the test battery during the study time period.

It is evident that (a) the frequency of positive test reactions differed markedly between CS and (b) that late readings (here: 4th day after start of test [D4]) partially performed were able to detect some additional positive reactions. (It cannot be excluded that a D4 reading was performed selectively when history was very suspect, when a positive reaction occurred to the respective brand specialty or in cases with doubtful reaction on D3 or earlier.)

The CS were classified according to presumed antigen groups [2] (Table 2). The pattern of cross-reactivity among the 9 CS tested is illustrated in Table 3. On the basis of the postulated marker function of budesonide, the reactions to amcinonide, triamcinolone acetonide or hydrocortisone 17-butyrate were compared to those to budesonide. In 43 patients simultaneous positive reactions to budesonide and at least one of the three other CS occurred: in 12 patients, positive reactions only to budesonide; and in the vast majority of 2168 patients, no positive reactions. The concordance between budesonide and the pooled other reactions was comparatively high with a kappa of 0.82 (95 % CI: 0.74–0.90).

On the basis of the assumption forming the foundations of the CE-DUR approach [13, 16] the frequency of contact allergy to CS was roughly estimated on a population level for Germany (Table 4). The main goal of the study was the estimation of the "relative incidences" (RI) for which the CE-DUR incidences form the numerator. As denominator of RI the annual prescription of CS topical products in million DDD, averaged over the 10-year time period, are presented in Table 3. Within this time the prescription of most CS remained relatively constant, while for others declines of an in part dramatic nature were observed [17], e. g. for amcinonide from 6.7 to 3.0 million DDD, for prednisolone from 91.4 to 50.4 million DDD and for dexamethasone (all salts) from 143 to 72.1 million DDD. On the right in Table 3 the calculated relative incidence is shown. In order to avoid redundancy, only the "medium" scenario is illustrated, as by multiplication (with 0.577 for the "conservative" or 2.38 for the "extreme") the other estimates can easily be derived and

further the "medium" scenario is considered the most appropriate [13].

Discussion

On the basis of the anti-inflammatory effects of CS, contact allergies to CS appear initially paradoxical, but are a well-verified phenomenon [1–3]. This study presents current clinical data on patch testing with CS, extrapolates this to the population level and particularly quantifies the CA risk for the first time using the population-based CA incidence as numerator and the exposure to the respective CS as denominator.

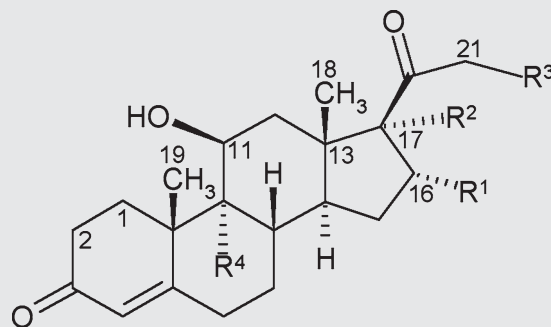
The relative frequency of positive test results with any test series depends greatly on the indication, i. e. the pre-selection of the patch test patients. Within the IVDK in 7.4 % of patients CA to (one of the) CS was considered possible and the test battery was applied, however, positive reactions were rare (Table 1). When observing the reaction profiles, it is evident, on the one hand, that the proportion of strongly positive reactions (++ or +++) among all positive reactions fulfills the expectations for an adequate allergen preparation. On the other hand, a very high proportion of doubtful (or very rarely: explicitly irritant) reactions whose dignity is unclear can be observed. It was, for example, presumed that persistent erythema for up to two days after removal of the test tape might reflect a rebound reaction after previous "blanching" by the CS [7]. Alternatively, the doubtful reactions might at least in part indicate a delayed appearing weakly positive (allergic) reaction, which is why some authors propose the necessity of late readings up to day 7 after the start of the test (among others [3, 18]). Therefore, in the case of CS even with otherwise guideline-conform [8,19] patch testing limited sensitivity and in our results a certain underestimation of prevalence must be expected. Complicating matters, the "ideal concentration" and the most suitable vehicle for the patch test are in part controversial. The "routine data" presented here cannot add new knowledge on this matter, as besides testing the CS battery no systematic diagnostics with threshold testing (as in the first version of the test battery [7]), ROAT or PUT were performed or documented.

Despite these limitations, at least in part, and most definitively for the allergens which relatively often lead to positive

Table 1: Allergens of the current DKG “corticosteroid test battery” and results of patients patch tested in the IVDK between 01/1995 and 12/2004 (based on the standard reading on day 3 after start of exposure; additionally in further patients readings were performed on day 4, see right column: number of additional positive reactions / numbers read).

Allergen CAS-Nr.	Abbr.	Test con- centration (%)	N (tested) read at day 3	?/IR	+	++/+++	% pos.	% pos. (stand.) 95 % CI	Reaction index [11]	Positivity ratio [11]	Day 4: further pos./read
Amcinonide 51022-69-6	AMCI	0.1	5925	183	54	40	1.6	1.3 (1.0–1.5)	–0.3	57.4	3/271
Hydrocortisone 50-23-7	HYCO	1	5940	35	16	3	0.3	0.3 (0.1–0.5)	–0.3	84.2	0/285
Triamcinolone acetoneide 76-25-5	TRIAM	0.1	5936	99	24	7	0.5	0.4 (0.3–0.6)	–0.5	77.4	1/282
Clobetasol 17-propionate 25122-46-7	CLOB	0.25	5677	142	20	4	0.4	0.3 (0.2–0.5)	–0.7	83.3	2/527
Hydrocortisone 17-butyrate 13609-67-1	HYBUT	0.1	5817	117	67	20	1.5	1.3 (1.0–1.6)	–0.1	77.0	2/394
Betamethasone 17-valerat 2152-44-5	BETA	0.12	5938	160	25	3	0.5	0.4 (0.2–0.6)	–0.7	89.3	0/279
Budesonide 51333-22-3	BUD	0.1	2260	60	29	28	2.6	2.1 (1.5–2.7)	–0.03	50.9	5/94
Prednisolone 50-24-8	PRED	1	2259	16	6	3	0.4	0.4 (0.1–0.7)	–0.3	66.7	3/270
Dexamethasone 2392-39-4	DEXA	1	2212	39	4	4	0.4	0.3 (0.1–0.5)	–0.7	50.0	0/74

All allergens in petrolatum.

Table 2: Structural differences of corticosteroids examined as well as further representatives (in *italics*).

Group	Substance	R ¹	R ²	R ³	R ⁴	Further
A	HYCO	H	OH	OH	H	
	PRED	H	OH	OH	H	DB on C1/C2
	<i>TIXOP</i>	<i>H</i>	<i>OH</i>	<i>S-CO-C(CH₃)₃</i>	<i>H</i>	
B	TRIAM	Ketal on C16/C17		OH	F	DB on C1/C2
	AMCI	Ketal on C16/C17		OH	F	DB on C1/C2
	BUD	Ketal on C16/C17		OH	H	DB on C1/C2
C	DEXA	◀CH ₃	OH	OH	F	DB on C1/C2
D1	BETA	CH ₃	O-CO-C ₄ H ₉	OH	F	DB on C1/C2
	CLOB	CH ₃	O-CO-C ₂ H ₅	Cl	F	DB on C1/C2 Keton on C11
	<i>MOMFU</i>	<i>CH₃</i>	<i>O-CO-furan</i>	<i>Cl</i>	<i>Cl</i>	<i>DB on C1/C2</i>
D2	HYBUT	H	O-CO-C ₃ H ₇	OH	H	
	<i>PREDCA</i>	<i>H</i>	<i>O-CO-O-C₂H₅</i>	<i>OH</i>	<i>H</i>	<i>DB on C1/C2</i>

TIXOP: tixocortol pivalate, MOMFU: mometasone furoate, PREDCA: prednicarbate, DB: double bond.

test reactions, the postulated pattern of cross-reactivity or the existence of antigenic groups were reproduced. In such comparisons not the theoretical maximum of 1 should be taken as the upper limit of the kappa coefficient, but a value of about 0.87, which is observed in synchronous double application of “established” allergens such as nickel sulfate or p-phenylenediamine [20]. By this the concordance observed here can be rated somewhat higher. The highest concordance is seen between budesonide and amcinonide (group B) and between budesonide and hydrocortisone 17-butyrate (group D2), see Table 3. This confirms other data [2, 3]. However, a similar consistent concordance can be seen between dexamethasone (group C) and betamethasone 17-valerate or clobetasol 17-propionate (both group D1), which does not conform to the postulated antigen pattern. However, with clinical data

it is often unclear if observed concordance is solely based on immunologic cross-reactivity, as previous exposure to the cross-reacting allergen and thus an independent sensitization usually cannot be ruled out. On this basis, true “immunologic” cross-reactivity might be overestimated [21]. This might be the cause of the unexpectedly high concordance between CS of groups C and D1. The above-mentioned diagnostic uncertainties naturally impair the extrapolation of clinical test results to the population level. Further this is based on several assumptions – even if empirically founded – so that morbidity estimates possess some uncertainty. The representation of three scenarios should do this justice. These uncertainties are – just as in the following discussion of the reliability of exposure documentation – probably similar for the individual allergens, so that the comparison of (relative)

incidences again appears sufficiently valid.

Exposure is represented here by the prescription data; with the exception of hydrocortisone, which was also available in a concentration of $\leq 0.25\%$ OTC during the study period leading to an underestimation of its exposure. In the WIdO data base private patients as well as hospital inpatients are not included, the latter probably of less importance in terms of numbers. This limitation does not exist for morbidity data which includes patients with private as well as statutory health insurance, so that RI may slightly be overestimated by about 16 %. As it is unclear, however, whether the prescription spectrum differs between statutory and private health insurance, the RI estimates were not generally reduced by 16 %. Thus a certain, comparably small uncertainty pertaining to the RI estimates cannot be excluded. On the other

Table 3: Pattern of cross-reactivity between the 9 corticosteroids, dichotomized into positive (+ to +++) and non-positive (neg., ?, IR) reactions. Cohen's kappa (95 % confidence interval).

Group	A		B			C	D 1		D 2
	HYCO	PRED	TRIAM	AMCI	BUD	DEXA	BETA	CLOB	HYBUT
HYCO		0.14 (0–0.39)	0.49 (0.32–0.66)	0.27 (0.16–0.37)	0.19 (0.06–0.32)	0.14 (0–0.39)	0.21 (0.06–0.37)	0.10 (0–0.24)	0.11 (0.03–0.20)
PRED			0.09 (0–0.25)	0.05 (0–0.15)	0.06 (0–0.14)	0.13 (0–0.37)	0.30 (0.03–0.56)	0 (0–0)	0.09 (0–0.21)
TRIAM				0.46 (0.35–0.57)	0.37 (0.22–0.51)	0.54 (0.29–0.79)	0.41 (0.25–0.57)	0.42 (0.25–0.59)	0.22 (0.12–0.32)
AMCI					0.61 (0.49–0.74)	0.40 (0.19–0.60)	0.28 (0.17–0.38)	0.25 (0.14–0.36)	0.22 (0.13–0.30)
BUD						0.24 (0.11–0.39)	0.24 (0.10–0.37)	0.19 (0.06–0.32)	0.64 (0.52–0.76)
DEXA							0.67 (0.41–0.92)	0.62 (0.34–0.90)	0.37 (0.17–0.56)
BETA								0.49 (0.32–0.66)	0.27 (0.17–0.39)
CLOB									0.26 (0.15–0.37)

Table 4: Frequency (annual incidence) of contact allergies to corticosteroids in Germany, 1995–2004, estimated by the CE-DUR method [13, 16], annual prescriptions (averaged over the 10-year time period) in million DDD as well as the relative incidence (RI) for the “medium” scenario as number of sensitization cases/ 100 000 DDD with associated 95 % confidence interval (CI).

Allergen	Annual incidence: scenario			Prescriptions (in million DDD)	Relative incidence (medium scenario)	
	“conservative“	“medium“	“extreme“		RI	(95 % CI)
Amcinonide	667	1155	2748	4.9	23.6	(8.9–38.3)
Hydrocortisone	132	228	543	≥ 24.1	0.9	(0.0–2.2)
Triamcinolone acetonide	226	392	933	27.5	1.4	(0.0–2.9)
Clobetasol 17-propionate	173	299	712	21.0	1.4	(0.0–3.2)
Hydrocortisone 17-butyrate	613	1062	2527	10	10.7	(3.7–17.7)
Betamethasone	193	335	797	60.4	0.6	(0.0–1.2)
Budesonide	1202	2082	4952	4.8 #47.2	43.2 #4.9	(24.4–62.0) #(2.8–7.0)
Prednisolone	185	320	762	59.9	0.5	(0.0–1.1)
Dexamethasone	166	288	686	86.1	0.3	(0.0–0.7)

For prescriptions “≥” denotes additional exposure due to OTC availability.
Budesonide perceived as marker: additional DDD of AMCI, TRIAM and HYBUT considered (see text).

hand we assume that the overestimation of exposure on the basis of prescription data that results from the actual, partly incomplete, use of the preparations does not differ among active agents with a similar indication and should thus not have a distorting effect on the comparison. In comparing the prevalences of clinical sensitization (Table 1) and the relative (in relation to exposure) incidences (RI, Table 4) it is remarkable that the CS

which often (> 1 %) cause positive reactions in patch test patients, i. e. amcinonide, hydrocortisone 17-butyrate and budesonide belong at the same time to the more rarely prescribed CS, so that the RI of these three CS diverge even more from the other CS whose RI is very low with < 1.5/100 000 DDD. Thus the previous estimation of the allergenic risk based exclusively on clinical data (e. g. in the guideline for topical dermatotherapy with glucocorticoids [22]) is confirmed as to the ranking but even further accentuated quantitatively. Budesonide takes on a special role, as it at present is not contained in any drug specially for treating the skin, but is used only for topical anti-inflammatory therapy of the respiratory and gastrointestinal tracts. In the context of the CS battery it serves as “marker allergen” for presumably related antigens of CS group B and several esters of group D2. Therefore the relatively high RI for budesonide should be put into perspective: When as exposure denominator not only the relatively small exposure to budesonide nasal spray (4.8 million DDD per year) is considered, but also DDDs of amcinonide, triamcinolone acetonide and hydrocortisone 17-butyrate are added, the RI decreases (Table 4). Even this RI is significantly higher than that of < 1.5 of most other CS. Cross-reactivity (of a small extent) must be considered in the interpretation of RI towards other CS. On the one hand CA to a particular CS may lead to intolerance of CS of the same or putatively cross-reaction group (clinically or in the patch test), which increases the significance. On the other hand, cross-reactivity can lead to overestimation of the CA risk of a particular CS, as presumably a proportion of the positive test reactions are not due to a primary sensitization towards this CS but to a primary CA towards a related CS, e. g. reactions to hydrocortisone 17-butyrate after sensitization to the also relatively frequently prescribed prednicarbate. Next to older CS active ingredients, at least towards the end of the study period newer CS were employed (million DDD in 2004 according to [14]), e. g. prednicarbate (36.8 million DDD), mometasone furoate (25.9 million DDD), methylprednisolone aceponate (17.2 million DDD), fluocinolone acetonide (9.5 million DDD) as well as – rarely – other active agents. At the time of the

last revision of the CS test battery, these CS were not commercially available as standardized test substances. For this reason they cannot be included in the risk assessment. At present only clinical case studies or series allow for a preliminary clue as to sensitization potential.

Conclusions

Contact allergies to CS are rare even in a selectively tested patient subgroup. The prevalence of sensitization is probably underestimated due to possible false negative reactions. If CA to CS is suspected, it is recommended to read the patch tests up to day 7. The relation of extrapolated sensitization incidences to the population-wide exposure (at least to the 86 % of the population with statutory health insurance) demonstrates clearly that sensitizations to the more “potent allergens” among the CS, i. e. amcinonide and hydrocortisone 17-butyrate are many times more frequent than to a number of other standard CS, which should be considered in making therapeutic choices.

Note

The following German centers of the IVDK contributed data to the analysis (in alphabetical order): Aachen (C. Schröder, H. Dickel, S. Erdmann), Augsburg (A. Ludwig), Berlin Charité (B. Laubstein, M. Worm, T. Zuberbier), Berlin UKRV (J. Grabbe, T. Zuberbier), Bielefeld (I. Effendy), Bochum (Ch. Szliska, M. Straube), Dortmund (B. Pilz, C. Pirker, K. Kügler, P.J. Frosch, R. Herbst), Dresden (G. Richter, P. Spornraft-Ragaller, R. Aschoff), Duisburg (J. Schaller), Erlangen (K.-P. Peters, M. Fartasch, M. Hertl, T.L. Diepgen, V. Mahler), Essen (H.-M. Ockenfels, U. Hillen), Freudenberg (Ch. Szliska), Gera (J. Meyer), Göttingen (J. Geier, Th. Fuchs), Halle (B. Kreft, D. Lübke, G. Gaber), Hamburg (D. Vieluf, M. Kiehn, R. Weißbecher), Hannover (T. Schaefer, Th. Werfel), Heidelberg (A. Schulze-Dirks, M. Hartmann, U. Jappe), Heidelberg AKS (E. Weisshaar, H. Dickel, T.L. Diepgen), Homburg/Saar (P. Koch), Jena (A. Bauer, M. Gebhardt, M. Kaatz, S. Schliemann-Willers, W. Wigger-Alberti), Kiel (J. Brasch), Krefeld (A. Wallerand, M. Lilie, S. Wassilew), Lübeck (J. Grabbe, J. Kreusch), Mannheim (Ch. Bayerl), Marburg (H. Löffler, I. Effendy), Munich LMU (B. Przybilla, P. Thomas, T. Oppel), Munich

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Conflicts of interest

None.

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