

ORIGINAL ARTICLE

Chronic hand eczema in Germany: 5-year follow-up data from the CARPE registry

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Background: The CARPE registry was set up in 2009 to prospectively investigate the management of patients with chronic hand eczema (CHE).

Objectives: To report comprehensive follow-up data from the CARPE registry.

Patients and methods: We investigated sociodemographic and clinical characteristics, provision of medical care, physician-assessed outcomes, and patient-reported outcomes (PROs). Data were collected between 2009 and 2016, with up to 5 years of follow-up, and are reported descriptively.

Results: Overall, 1281 patients were included in the registry (53.7% female). Mean age was 47.0 years. Of the patients, 793 and 231 completed the 2-year follow-up and 5-year follow-up, respectively. At baseline, 5.4% had changed or given up their job because of CHE, the average duration of CHE was 6.1 years, and, in 22.4%, the CHE was severe according to physician global assessment. Systemic treatment (alitretinoin, acitretin, and methotrexate) was prescribed at least once to 39.0% of the patients during the course of the follow-up. Disease severity, quality of life and treatment satisfaction improved over time, and the proportion of patients receiving systemic treatments decreased.

Conclusions: Under continued dermatological care, substantial improvements in disease severity and PROs over time was achieved during the course of the CARPE registry, even in patients with long-standing and severe hand eczema.

KEYWORDS

hand eczema, quality of life, registry, treatment

1 | INTRODUCTION

Hand eczema (HE) is a common inflammatory skin condition of the hands, clinically characterized by redness, vesicles, oedema, scaling,

infiltration of the skin, fissures, hyperkeratosis, and erosions.¹ According to a systematic review of studies performed between 1964 and 2007, the 1-year and lifetime prevalences are 10% and 15%, respectively, in the adult general population.² On the basis of 7 studies included in this systematic review, the median incidence rate was estimated to be 5.5 cases/1000 person-years. Female sex, contact allergy,

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wet work and atopic eczema were identified as the main risk factors. Incidence rates are much higher in occupational populations at risk, such as nurses³ and hairdressing apprentices.⁴ The negative impact of HE on health-related quality of life (HR-QoL) has been documented, and has been found to be comparable to the impact of asthma or psoriasis.⁵ Furthermore, a relationship between HR-QoL impairment and disease severity has been shown.⁶

Experts estimate that the proportion of severe chronic HE (CHE) ranges between 5% and 10% of all cases of HE.⁷ In contrast to HE in general, however, epidemiological data pertaining to CHE are scarce. A recent study using data from the Clinical Practice Research Datalink in the United Kingdom found a 10-year CHE period prevalence of 0.14%.⁸ The 10-year period prevalence of corticosteroid-refractory CHE was even lower (0.072%). Despite the fact that this study had to rely on records from general practitioners only, it is likely that only a fraction of people with self-reported HE seek medical care.

The characteristics of patients with CHE who are receiving specialist dermatological care are largely unknown. A variety of therapeutic options (topical treatments, ultraviolet [UV] therapy, and systemic therapies) exist for the management of CHE, but there is a scarcity of data on the long-term effectiveness and safety of different therapies in patients with CHE. In light of this situation, the CARPE (Chronisches Handekzem-Register zum Patienten-Langzeitmanagement) registry was set up in 2009 in Germany under the auspices of the German Dermatological Society (Deutsche Dermatologische Gesellschaft),⁹ and was later also implemented in Switzerland.¹⁰ Previously, descriptive baseline data have been reported.^{9,11} Meanwhile, a 5-year follow-up has been completed. Therefore, in this article, our aim is to report comprehensive prospective 5-year follow-up data for patients recruited in the German CARPE registry.

2 | MATERIALS AND METHODS

No formal sample size calculation was performed before the registry started. Overall, 99 dermatology centres in Germany (either in dermatologists' practices [$n = 71$] or in secondary care in hospital clinics [$n = 28$]) recruited patients for the CARPE registry. Study design and methodological aspects of the registry have been previously reported in detail.^{9,11} The following patient inclusion criteria were applied: (1) disease duration of >3 months, or >2 flares within the previous 12 months; (2) previous treatment with topical corticosteroids; (3) no long-lasting healing under adequate topical treatment including corticosteroids; and (4) no other dominating active severe skin diseases or acute skin infections.

After inclusion (T_0), patients were followed-up in prespecified time intervals after 3 (T_1), 6 (T_2), 12 (T_3), 18 (T_4) and 24 (T_5) months. According to an amendment of the original study protocol, those intervals were extended to 36 (T_6), 48 (T_7) and 60 (T_8) months for all patients who did not withdraw their agreement to participate. The documentation in the CARPE registry was based on a physician questionnaire and a patient questionnaire; the parameters assessed at each visit are shown in Table S1. CHE severity was assessed both by the physician using physician global assessment (PGA) supported by a validated photographic guide,¹² and by the patient on a 10-point

numerical rating scale. Another physician severity rating was performed with the Occupational Contact Dermatitis Disease Severity Index (ODDI), which includes an assessment of impairments in work-related activities.^{13,14} The Erlangen atopy score was used to assess atopy.^{15,16} Six diagnostic categories were used to classify hand eczema, representing both aetiological (irritant contact dermatitis, allergic contact dermatitis [ACD], and atopic HE) and morphological (vesicular dermatitis, hyperkeratotic dermatitis, and fingertip dermatitis) categories. HR-QoL was measured with the German version of the Dermatology Life Quality Index (DLQI).^{17,18} Because new research has shown that there are several limitations in using the DLQI in patients with CHE, we report adjusted DLQI scoring, which is assumed to be adequate in a population of CHE patients (only 6 items are scored, and the range of the adjusted DLQI is 0-15).¹⁹ In order to overcome those limitations of the DLQI, the Quality of Life in Hand Eczema Questionnaire (QOLHEQ)²⁰ was later introduced into the registry. The QOLHEQ is a disease-specific HR-QoL instrument that assesses HR-QoL of HE patients in 4 domains: (1) symptoms, (2) emotions, (3) functioning, and (4) treatment and prevention.

Data were entered into and stored in a Microsoft Access 2003 database. Data entry was performed twice, and plausibility checks were performed as measures of quality assurance. Analyses of quantitative and qualitative variables were performed with SPSS (version 23) for Windows. Quantitative variables with interval scaling were summarized as mean and SD. Ordinally or nominally scaled variables were summarized as counts (n) and percentages. Complete case analysis was performed for each variable of interest; that is, observations with missing data were excluded separately for each analysis.

3 | RESULTS

3.1 | Recruitment and flow of patients assessed over time

As of March 2016, 1281 patients had been recruited into the CARPE registry; $n = 492$ (38.4%) in dermatologists' practices, and $n = 789$ (61.6%) in hospital clinics. Of the 1281 patients initially included, after 2 years 923 (65.3%) were eligible for the extended follow-up period of 5 years. Eighty-seven of those refused to participate in the extended follow-up. Finally, 281 (33.6%) patients completed the 5-year follow-up. Overall, 735 (57.4%) patients had dropped out of the CARPE registry and 226 (17.6%) had not shown up to the final visit after 5 years until the termination of the CARPE registry at the end of March 2016. The complete patient assessment flow, including no-shows and drop-outs, is shown in Figure S1.

3.2 | Sociodemographic characteristics at baseline

Overall, 53.7% of the patients registered in the CARPE registry were female. Their mean age was 47.0 years (SD 13.6 years; median 48.7 years; range 18-84 years). The mean body mass index (BMI) was 26.8 kg/m² (SD 4.7 kg/m²; range 17.3-49.2 kg/m²). Patients suffered from CHE for a mean duration of 6.1 years (SD 7.9 years). Both age (46.2 years, SD years 12.9 vs 47.8 years, SD 14.0 years) and BMI

TABLE 1 Demographic characteristics at T₀

	Males (n = 593)	Females (n = 688)	Total (N = 1281)
Age (years), mean (SD)	47.86 (12.9)	46.22 (14.0)	46.98 (13.6)
BMI, mean (SD)	27.27 (4.0)	26.28 (5.2)	26.74 (4.7)
Duration of HE (in years), mean (SD)	5.93 (7.9)	6.31 (7.9)	6.14 (7.9)
Inpatient treatment before first carpe visit, % (n)	34.8 (202)	32.5 (220)	33.6 (422)
Dermatologist's report, % (n)	66.2 (387)	65.5 (441)	65.8 (828)
Occupational disease notified, % (n)	27.1 (155)	25.5 (171)	26.2 (326)
Sick leave in the last 12 months, % (n)	38.0 (211)	32.9 (210)	35.3 (421)
Sick leave at the time of the visit, % (n)	26.2 (148)	23.1 (150)	24.5 (298)
Given up occupation/changed occupation, % (n)	5.8 (34)	5.0 (34)	5.4 (68)

BMI, body mass index; HE, hand eczema.

(26.3 kg/m², SD 5.2 kg/m² vs 27.3 kg/m², SD 4.0 kg/m²) of women were lower than those of men. The mean duration of CHE was similar between males and females. Demographic characteristics are shown in detail in Table 1.

At baseline, *n* = 1056 (82.8%) of the recruited patients were employed. The most frequent occupational groups were nurses and healthcare workers (21.0%), metalworkers and electricians/mechanics (17.8%), and food and catering workers (12.1%). The occupational group of nurses and healthcare workers was dominated by females (90%), and the same was true for food and catering (62%). Males dominated among metalworkers and electricians/mechanics (94%).

Overall, 33.6% of the participants had ever received inpatient treatment, either in an acute care hospital or in a rehabilitation facility. A dermatologist's report to the compulsory statutory accident insurance in Germany was issued for 65.8% of the participants and an occupational disease was notified for 26.2% of the participants in the preceding 12 months. Of the patients, 5.4% had changed or given up their occupation because of their CHE. The rate of sick leave because of hand eczema in the past 12 months was 35.3%, and 24.5% of the patients were currently unable to work.

3.3 | Clinical characteristics at baseline

In the 12 months before inclusion in the CARPE registry, a patch test had been performed in 54.6% of all patients, and contact allergy was found in 48.5%. The most prevalent allergens were nickel (23.9%), fragrance mix I (16.9%), cobalt (13.6%), and chromium (12.9%). Whereas

the 3 most common allergens were more prevalent in females, chromium was the only allergen that was more common in males. Table 2 shows the 10 most frequent contact allergies that were found to be of clinical relevance for CHE. Prick testing was performed in 42.3% of the patients. Immediate-type hypersensitivity to latex with clinical relevance for CHE was found in 5.4% (*n* = 30) of those who had been prick tested in the previous 12 months (*n* = 542).

Mycological diagnostic investigation was performed in 38.4% of the patients; the findings were negative in 81.4% of the tested patients, positive in 8.0%, and unclear in 10.7%. The most frequent localization was the palm of the hand (83.5%), followed by the interdigital web spaces (64.8%) and the back of the hand (48.6%). In the overwhelming majority of cases (96.1%), both hands were affected by CHE, in 2.8% CHE was localized to the right hand, and in only 0.8% CHE was localized to the left hand. Concomitant eczema on the feet was present in 27.3% of the patients; eczema at other body sites was present in 23.6%. Itching was present in 80.1% of the patients. Females reported moderate or severe itching more often than males (50.7% vs 42.4%).

Irritant contact dermatitis was the most frequent diagnosis, seen in 583 patients (45.5%), followed by atopic HE (35.8%), hyperkeratotic-rhagadiform HE (32.1%), vesicular HE (25.8%), ACD (21.1%), and fingertip dermatitis (7.2%). An atopic skin diathesis was present in 43.5% of the patients, was absent/unlikely in 46.8%, and was uncertain in 9.7%. As can be seen in Table 3, the most common skin-stressing exposures were wet work and wearing gloves. Overall,

TABLE 2 Top 10 type IV sensitizations in chronic hand eczema patients

Most frequent allergens	Females (N = 366)		Males (N = 334)		Total (N = 700)	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Nickel sulfate	134	36.6	33	9.9	167	23.9
Fragrance mix I	67	18.3	48	14.4	115	16.9
Cobalt chloride	58	15.8	37	11.1	95	13.6
Potassium dichromate	36	9.8	48	14.4	84	12.0
<i>Myroxylon pereirae</i> (balsam of Peru)	37	10.1	36	10.8	73	10.4
Thiuram mix	44	12.0	22	6.6	66	9.4
Methyldibromo glutaronitrile	19	5.2	23	6.9	42	6.0
Colophonium	18	4.9	24	7.2	42	6.0
Methylchloroisothiazolinone/methylisothiazolinone	25	6.8	15	4.5	40	5.7
Lanolin alcohol	19	5.2	14	4.2	33	4.7

TABLE 3 Exposures

	At work	Leisure time	At work and leisure time	None
Wet work				
<i>n</i>	325	168	440	348
%	25.4	13.1	34.3	27.2
Cleansing agents				
<i>n</i>	206	222	452	401
%	16.1	17.3	35.3	31.3
Disinfectants				
<i>n</i>	433	40	84	724
%	33.8	3.1	6.6	56.5
Water-based cooling lubricants				
<i>n</i>	183	13	25	1060
%	14.3	1.0	2.0	82.7
Solvents				
<i>n</i>	238	26	39	978
%	18.6	2.0	3.0	76.3
Technical oils/fats				
<i>n</i>	267	26	58	930
%	20.8	2.0	4.5	72.6
Mechanical strain				
<i>n</i>	269	77	341	594
%	21.0	6.0	26.6	46.4
Preservatives				
<i>n</i>	105	37	113	1026
%	8.2	2.9	8.8	80.1
Wearing gloves				
<i>n</i>	393	136	478	274
%	30.7	10.6	37.3	21.4

78.6% of the patients were using gloves at work, at leisure time, or in both settings.

3.4 | Medication

Overall, 51.2% of the patients had received topical corticosteroid treatment at the time of their first CARPE visit (T_0), 23.1% with potent corticosteroids and 5.9% with very potent corticosteroids. Figure S2A shows the course of topical treatment with corticosteroids during the course of the CARPE registry. At T_8 , only 29.9% of the patients had received a prescription of topical corticosteroids. The course of any other topical therapy during the CARPE registry is shown in Figure S2B. The rates of prescription of urea (35.2% at T_0) and tannin (22.0% at T_0) rose slightly until T_8 (47.3% and 32.0%, respectively). The prescription of salicylic acid fell from 9.4% at T_0 to 3.6% at T_8 . The rates of UV therapy prescription are shown in Figure S2C. The strongest decrease was found in the prescription of psoralen plus UVA (PUVA) cream, which decreased from 23.0% at T_0 to 2.5% at T_8 . The prescription rate for bath PUVA and for other light therapies was <2.0%, and the prescription of other systemic PUVA therapies was negligible. The prescription rate for any systemic therapy during the CARPE registry is shown in Figure S2D. It can be seen that the prescription of any systemic therapy declined from 31.1% at T_0 to 13.5%

at T_8 . Overall, $n = 499$ patients (39.0%) were treated with alitretinoin, acitretin or methotrexate during the course of the CARPE registry.

3.5 | Response analysis

Because a relevant number of patients were lost to follow-up, we performed a responder/non-responder analysis in relation to baseline characteristics of the sample. The analysis was performed for the response until the regular follow-up after 2 years (T_5) and until the end of the extended follow-up after 5 years (T_8). The results are shown in Table S2. We found no significant differences between responders and non-responders concerning sex, age, severity of HE (PGA), or HR-QoL (DLQI). However, the proportion of patients with a notified occupational disease was higher in the responder group at T_5 (32.6% vs 15.6%) and at T_8 (38.7% vs 22.7%). The same was true for patients with the diagnosis of ACD (T_5 , 24.1% vs 16.2%; and T_8 , 28.5% vs 19.0%). On the other hand, the proportion of patients on sick leave at the visit or with the diagnosis of 'vesicular HE' was significantly lower in the responder group at T_5 and T_8 .

3.6 | Adverse events

Over the whole 5-year period, 128 patients reported at least 1 adverse event related to a prescription drug. Of those adverse events, 56.5% were reported to be mild, 35.7% moderate, and 7.8% severe. In 45.4%, the adverse event was likely to be associated with a specific drug, and for 27.1% of the events this association was confirmed. Most of the adverse events were seen to be associated with alitretinoin (73.0%) or ciclosporin (12.8%).

3.7 | Severity of CHE and HR-QoL impairment

As shown in Figure 1, the majority of CHE patients had moderate (45.9%) or severe (22.4%) skin lesions at the time of inclusion in the CARPE registry according to PGA. The severity decreased steadily down to a level of 17.9% moderate cases and only 2.2% severe cases at T_8 . At the same time, the patients' self-rated severity (on a scale from "0: no lesions" to "10: very severe lesions") declined from a mean severity of 4.9 (SD 2.5) to a value of 2.4 (SD 2.2) (Figure 2). The self-rated severity decreased from 4.9 (SD 2.7) to 3.9 (SD 2.2) at 3-month follow-up, and followed a linear trend, decreasing to 3.6 (SD 2.3) at T_2 , 3.3 (SD 2.4) at T_3 , and 3.0 (SD 2.3) at T_4 ; after 5 years of follow-up (T_8), the self-rated severity was at 2.4 (SD 2.2). A similar trend was seen with impairments in HR-QoL (also shown in Figure 2). The Rasch-adjusted DLQI values decreased from a mean of 5.0 (SD 3.2) at T_0 to 3.7 (SD 2.9) at T_1 , 3.5 (SD 2.8) at T_2 , and 2.6 (SD 2.8) at T_8 . In line with these results, the mean number of CHE flares decreased throughout the course of the CARPE registry from 0.49 (SD 0.56) at T_0 to 0.20 (SD 0.36) at T_8 . The same was true for persisting CHE, which is shown in Table 4.

Disease severity as assessed with the ODDI (Figure S3A) showed a similar course as assessed with PGA. Impairments in work-related activities decreased, as can be seen in Figure S3B: at T_0 , only 3.8% of the patients reported no work-related limitations, but this proportion increased to 42.1% at T_8 , whereas the proportion of patients with

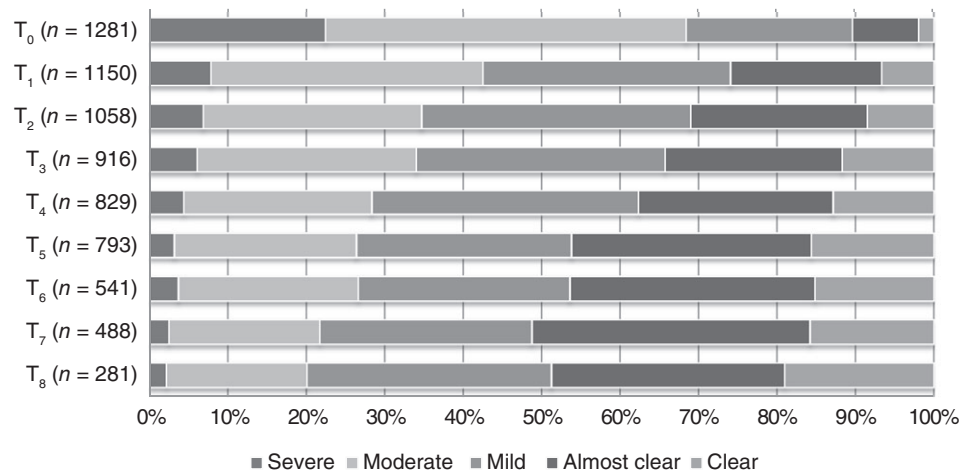


FIGURE 1 Severity of chronic hand eczema at each visit rated by the physician

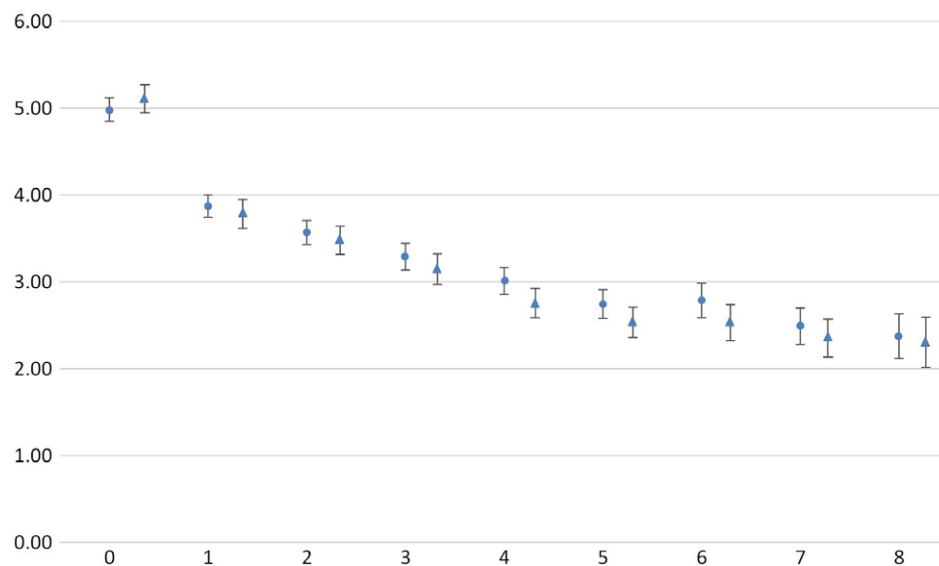


FIGURE 2 Severity of chronic hand eczema (circles) and mean Dermatology Life Quality Index values (triangles; adjusted according to Reference¹⁹), both as rated by the patient, with 95% CIs

severe or very severe limitations decreased from 10.8% at T₀ to 0.7% at T₈.

According to the definition of Hongbo et al,²¹ in 308 patients (27.8%) the CHE had a very large effect on HR-QoL, and in 63 (5.0%) the effect was extremely large at the time of inclusion in the CARPE registry. According to the QOLHEQ, the HR-QoL impairments were strongest in the areas of symptoms (mean 25.5) and functional (mean 26.1) impairments, whereas impairments because of emotions (mean 5.2) and because of treatment and prevention (mean 15.5) were less intense.

As shown in Figure S4A, the number of patients reporting side-effects declined during the course of the CARPE registry. Also the amount of patients who reported the treatment to be time-consuming declined (Figure S4B). Figure S4C shows that treatment satisfaction increased until T₇ and then was quite stable at T₈. Interestingly, the number of patients reporting not being able to perform treatment

according to recommendations increased during the course of the CARPE registry (Figure S4D). The number of visits to a dermatologist in the past 12 months decreased strongly after inclusion into the CARPE registry, and was then quite stable (Figure 3). The same trend was seen regarding visits to a general practitioner (data not shown).

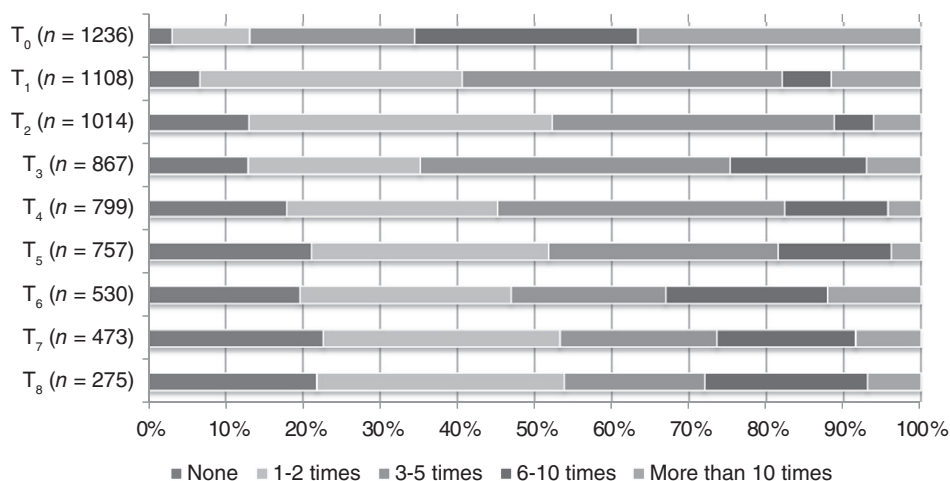
4 | DISCUSSION

This article contains a comprehensive description of the patients included in the CARPE registry in terms of their clinical and demographic characteristics, and patient-reported outcomes and therapies used in the management of CHE. Although these data have been reported for baseline previously,^{10,11} the prospective follow-up data up to 5 years are novel. We are not aware of any other study that has investigated a cohort of patients with CHE for such a long period of

TABLE 4 Chronic hand eczema (CHE) flares and persistent hand eczema

	Number of CHE flares (per month since last visit)			Persisting hand eczema		Total n
	Mean	SD	n	n	%	
T ₀ ^a	0.49	0.56	413	857	67.5	1270
T ₁	0.54	0.72	643	497	43.6	1140
T ₂	0.47	0.71	603	444	42.4	1047
T ₃	0.32	0.51	577	333	36.6	910
T ₄	0.32	0.67	530	294	35.7	824
T ₅	0.28	0.48	542	247	31.3	789
T ₆	0.24	0.45	352	184	34.3	536
T ₇	0.19	0.36	324	159	32.9	483
T ₈	0.20	0.36	186	89	32.4	275

^a Per month in the past 12 months.

**FIGURE 3** Visiting a dermatologist in the past 12 months as reported by the patient

time, with data collected for all topical, UV and systemic therapies, and an assessment of disease burden from both the doctors' and patients' perspectives.

There were significant differences between responders and non-responders at T₅ and T₈, indicating that patients with a notified occupational skin disease were more likely to respond. An explanation for this could be that those patients are more often seen by their dermatologist, so the CARPE visits do not represent an additional burden of assessment for them. This may also be the reason why the proportion of ACD was higher and the proportion of vesicular HE was lower in the responder group, which mirrors the diagnostic pattern in patients with occupational diseases notified in the CARPE registry (data not shown).

There is a large body of literature pertaining to HE, but little research has been conducted in CHE. The characteristics of patients included in the CARPE registry are largely in line with other data reported from studies performed in populations with CHE, all of which were non-interventional studies on alitretinoin. The TOCCATA study was the first study to investigate the treatment of CHE with oral alitretinoin in Germany, and included 680 patients with a mean age of 50 years.²² In the TOCCATA study, 56% of the patients were male, the mean duration of CHE was 7 years, and CHE was graded as severe by PGA in 65% of patients. The real-world FUGETTA study

investigated the impact of alitretinoin on HR-QoL in patients with CHE, and included 658 patients (52% male) with a mean age of 49 years.²³ Approximately 80% suffered from moderate-to-strong pruritus, and 83% of the CHE cases were rated as severe by PGA. In another real-world observational study, the PASSION study,²⁴ the mean age of the 631 included patients was 49 years, 48% of the patients were male, and 62% of CHE cases were rated as severe by PGA. Although, in terms of age, sex, and duration, the results are quite comparable, the severity seems to be slightly milder in the CARPE registry, in which 22.4% of patients were reported to have severe disease according to PGA, and 45.9% showed moderate severity.

The main findings of the descriptive analysis of the follow-up data presented in this article are as follows:

- Both objective disease severity and subjective disease severity decreased over time.
- HR-QoL improved over time, but remained stable after the second year of follow-up.
- The percentage of patients receiving systemic treatments (except antihistamines) decreased over time.
- The percentage of patients who reported side-effects or regarded the treatment as time-consuming decreased over time, while treatment satisfaction increased.

- The percentage of patients not being able to put treatment recommendations into practice increased over time.
- Healthcare utilization as measured by visits to general practitioners and dermatologists decreased after inclusion in the CARPE registry.

The overall picture is that CHE improves substantially over time, whether considered clinically or from the patients' own perception. Three main reasons may account for this finding. First, the regular visits may improve CHE through psychological effects of monitoring and feedback, which means that the CARPE registry itself has an interventional effect. Second, the regular visits also mean that there is room to optimize both treatment and the prevention of disease progression. Third, patients with difficult-to-treat CHE may have been more likely to have dropped out from the CARPE registry. On the other hand, the proportion of patients who reported not being able to fully implement treatment recommendations increased over time, which may indicate that patients with difficult-to-treat CHE are more likely to remain in the CARPE registry. In fact, both types of selection bias may operate at the same time. Either way, the loss to follow-up, particularly during the extended follow-up period after the second year, is a limitation of the CARPE registry. Another possible limitation may be the impact of large and highly specialized centres, which were overrepresented in the CARPE registry in comparison with their service share in the German health system. Some expensive or time-consuming treatment regimens may be primarily prescribed in such specialized centres. For instance, the omission of data from the CARPE centre that contributed the largest number of patients means that the prescription rate of PUVA cream at T₀ decreased from 23.0% to 14.3%. Such aspects should be the focus of further reports on the CARPE data.

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Conflict of interest

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Sanofi. R. Ofenloch and A. Heinrich declare no potential conflict of interests.

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REFERENCES

- Coenraads PJ. Hand eczema. *N Engl J Med*. 2012;367:1829-1837.
- Thyssen JP, Johansen JD, Linneberg A, Menne T. The epidemiology of hand eczema in the general population—prevalence and main findings. *Contact Dermatitis*. 2010;62:75-87.
- Visser MJ, Verberk MM, van Dijk FJ, Bakker JG, Bos JD, Kezic S. Wet work and hand eczema in apprentice nurses; part I of a prospective cohort study. *Contact Dermatitis*. 2014;70:44-55.
- Foss-Skiftesvik MH, Winther L, Johnsen CR, Zachariae C, Johansen JD. Incidence of skin and respiratory diseases among Danish hairdressing apprentices. *Contact Dermatitis*. 2017;76:160-166.
- Moberg C, Alderling M, Meding B. Hand eczema and quality of life: a population-based study. *Br J Dermatol*. 2009;161:397-403.
- Agner T, Andersen KE, Brandão FM, et al. Hand eczema severity and quality of life: a cross-sectional, multicentre study of hand eczema patients. *Contact Dermatitis*. 2008;59:43-47.
- Diepgen TL, Andersen KE, Chosidow O, et al. Guidelines for diagnosis, prevention and treatment of hand eczema. *J Dtsch Dermatol Ges*. 2015;13:e1-e22.
- Crane MM, Webb DJ, Watson E, Cunliffe T, English J. Hand eczema and steroid-refractory chronic hand eczema in general practice: prevalence and initial treatment. *Br J Dermatol*. 2017;176:955-964.
- Apfelbacher CJ, Akst W, Molin S, et al. CARPE: a registry project of the German Dermatological Society (DDG) for the characterization and care of chronic hand eczema. *J Dtsch Dermatol Ges*. 2011;9:682-688.
- Cazzaniga S, Apfelbacher C, Diepgen T, et al. Patterns of chronic hand eczema: a semantic map analysis of the CARPE registry data. *Br J Dermatol*. 2017;178:229-237.
- Apfelbacher C, Molin S, Weisshaar E, et al. Characteristics and provision of care in patients with chronic hand eczema: updated data from the CARPE registry. *Acta Derm Venereol*. 2014;94:163-167.
- Coenraads PJ, van der Walle H, Thestrup-Pedersen K, et al. Construction and validation of a photographic guide for assessing severity of chronic hand dermatitis. *Br J Dermatol*. 2005;152:296-301.
- Curr N, Dharmage S, Keegel T, Lee A, Saunders H, Nixon R. The validity and reliability of the occupational contact dermatitis disease severity index. *Contact Dermatitis*. 2008;59:157-164.
- Ofenloch RF, Diepgen TL, Popielnicki A, et al. Severity and functional disability of patients with occupational contact dermatitis: validation of the German version of the Occupational Contact Dermatitis Disease Severity Index. *Contact Dermatitis*. 2015;72:84-89.
- Diepgen TL, Fartasch M, Hornstein OP. Evaluation and relevance of atopic basic and minor features in patients with atopic dermatitis and in the general population. *Acta Derm Venereol Suppl (Stockh)*. 1989;144:50-54.
- Diepgen TL, Sauerbrei W, Fartasch M. Development and validation of diagnostic scores for atopic dermatitis incorporating criteria of data quality and practical usefulness. *J Clin Epidemiol*. 1996;49:1031-1038.
- Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)—a simple practical measure for routine clinical use. *Clin Exp Dermatol*. 1994;19:210-216.
- Augustin M, Zschocke I, Lange S, Seidenglanz K, Amon U. Lebensqualität bei haut-erkrankungen: vergleich verschiedener lebensqualitäts-fragebögen bei psoriasis und atopischer dermatitis. *Hautarzt*. 1999;50:715-722.
- Ofenloch RF, Diepgen TL, Weisshaar E, Elsner P, Apfelbacher CJ. Assessing health-related quality of life in hand eczema patients: how

- to overcome psychometric faults when using the dermatology life quality index. *Acta Derm Venereol*. 2014;94:658-662.
20. Ofenloch RF, Weisshaar E, Dumke AK, Molin S, Diepgen TL, Apfelbacher C. The quality of life in hand eczema questionnaire (QOLHEQ): validation of the German version of a new disease-specific measure of quality of life for patients with hand eczema. *Br J Dermatol*. 2014;171:304-312.
21. Hongbo Y, Thomas CL, Harrison MA, Salek MS, Finlay AY. Translating the science of quality of life into practice: what do dermatology life quality index scores mean. *J Invest Dermatol*. 2005;125:659-664.
22. Diepgen TL, Pfarr E, Zimmermann T. Efficacy and tolerability of alitretinoin for chronic hand eczema under daily practice conditions: results of the TOCCATA open study comprising 680 patients. *Acta Derm Venereol*. 2012;92:251-255.
23. Augustin M, Thaci D, Kamps A. Impact on quality of life of alitretinoin in severe chronic hand eczema: FUGETTA real-world study. *J Dtsch Dermatol Ges*. 2016;14:1261-1270.
24. Thaci D, Augustin M, Westermayer B, Kamps A, Hennig M. Effectiveness of alitretinoin in severe chronic hand eczema: PASSION, a real-world observational study. *J Dermatol Treat*. 2016;27:577-583.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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ONLINE SUPPLEMENTARY MATERIAL

TABLE S1: PARAMETERS ASSESSED AT EACH CARPE VISIT

	T0	T1 - T5	T6 - T8
Physician questionnaire			
diagnosis of CHE (aetiological and morphological)	x		
diagnostic parameters (including allergies, atopy, sick leave...)	x		
severity of CHE (PGA)	x	x	x
occupational limitations (ODDI)	x	x	x
past treatment (topical, UV therapy, systemic treatment)	x	x	x
prescribed treatment (topical, UV therapy, systemic treatment)	x	x	x
reasons for terminating systemic treatment	x	x	x
adverse events		x	x
Patient questionnaire			
Demographics	x		
atopy (self and family)	x		
inability to work	x	x	x
severity (NRS score)	x	x	x
exposures	x	x	x
perception of treatment regime	x	x	x
HRQOL (DLQI)	x	x	x
HRQOL (QOLHEQ)			x

CHE Chronic Hand Eczema; DLQI Dermatology Life Quality Index; HRQOL Health-Related Quality of Life; NRS Numeric Rating Scale; ODDI Occupational Contact Dermatitis Disease Severity Index; PGA Physician Global Assessment; QOLHEQ Quality of Life in Hand Eczema Questionnaire

Table S2: Responder analysis for response after 2 years (T₅) and 5 years (T₈) of follow-up

	response after 2 years (T ₅)				response after 5 years (T ₈)			
	non-responder (n=488)		responder (n=793)		non-responder (n=1000)		responder (n=281)	
	n	%	n	%	n	%	n	%
sex (female)	262	53.7%	426	53.7%	535	53.5%	153	54.4%
in-patient treatment before	163	34.1%	259	33.2%	323	32.9%	99	36.1%
dermatologist's report	316	66.5%	512	65.4%	635	64.7%	193	69.7%
occupational disease notified	73	15.6%	253	32.7%	220	22.7%	106	38.7%
sick leave last 12 month	184	40.8%	237	31.9%	331	35.7%	90	33.7%
sick leave at visit	144	31.0%	154	20.5%	254	26.9%	44	16.3%
occupation changed or given up	29	6.1%	39	5.0%	55	5.6%	13	4.8%
Irritant contact dermatitis	216	44.3%	367	46.3%	464	46.4%	119	42.3%
Atopic hand eczema	189	38.7%	270	34.0%	371	37.1%	88	31.3%
Allergic contact dermatitis	79	16.2%	191	24.1%	190	19.0%	80	28.5%
Vesicular hand eczema	151	30.9%	180	22.7%	288	28.8%	43	15.3%
Hypercerat.-rhagadif. hand eczema	141	28.9%	270	34.0%	326	32.6%	85	30.2%
Fingertip dermatitis	39	8.0%	53	6.7%	77	7.7%	15	5.3%
age (mean, SD)	45.9 (14.0)		47.6 (13.2)		46.8 (13.8)		47.5 (12.8)	
duration of HE (mean, SD)	6.0 (8.4)		6.2 (7.6)		6.0 (8.0)		6.5 (7.4)	
PGA (mean, SD)	2.3 (1.0)		2.2 (0.9)		2.2 (1.0)		2.2 (0.9)	
DLQI* (mean, SD)	5.3 (3.3)		4.8 (3.0)		5.1 (3.2)		4.6 (3.0)	

Bold printed values indicate significant differences between responders and non-responders (Bonferroni adjusted $p < 0.05/16$)

*Rasch adjusted according to Ofenloch et al. (21)

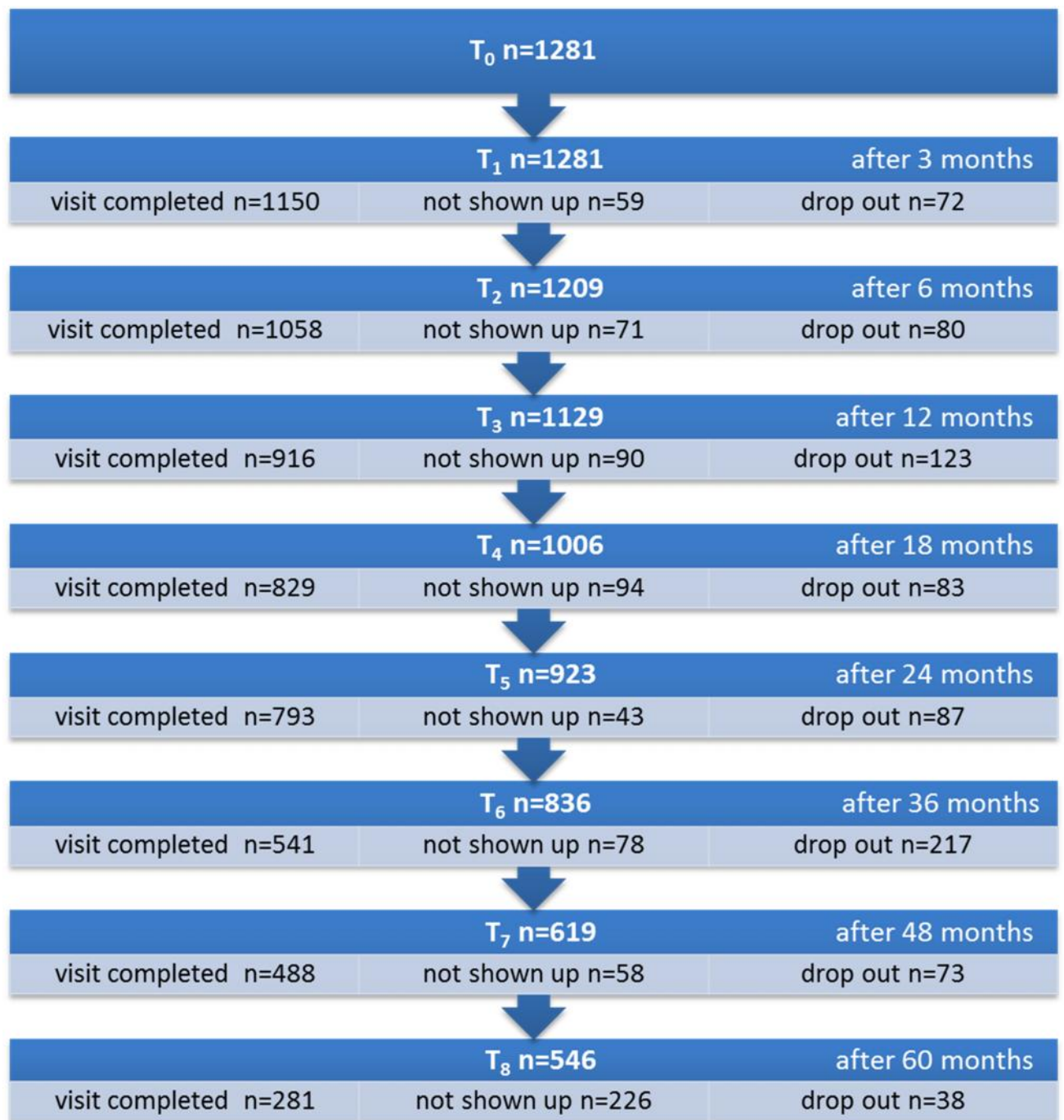


FIGURE S1: PATIENT-FLOW INCLUDING DROP OUTS

Figure S1 shows the flow of patient assessment for each visit in CARPE (T0-T5) including extended follow-up (T6-T8). At Baseline (T0) n=1281 subjects were included into the registry. All of them were eligible for follow up at T1, however n=72 subjects were dropouts at the second visit (T1) because of withdrawing consent or for other reasons (e.g. death). Further n=59 subjects didn't show up to the second visit but were still eligible for later visits. Overall n=1150 subjects completed T1 resulting in n=1209 subjects eligible for T2 (1150+59).

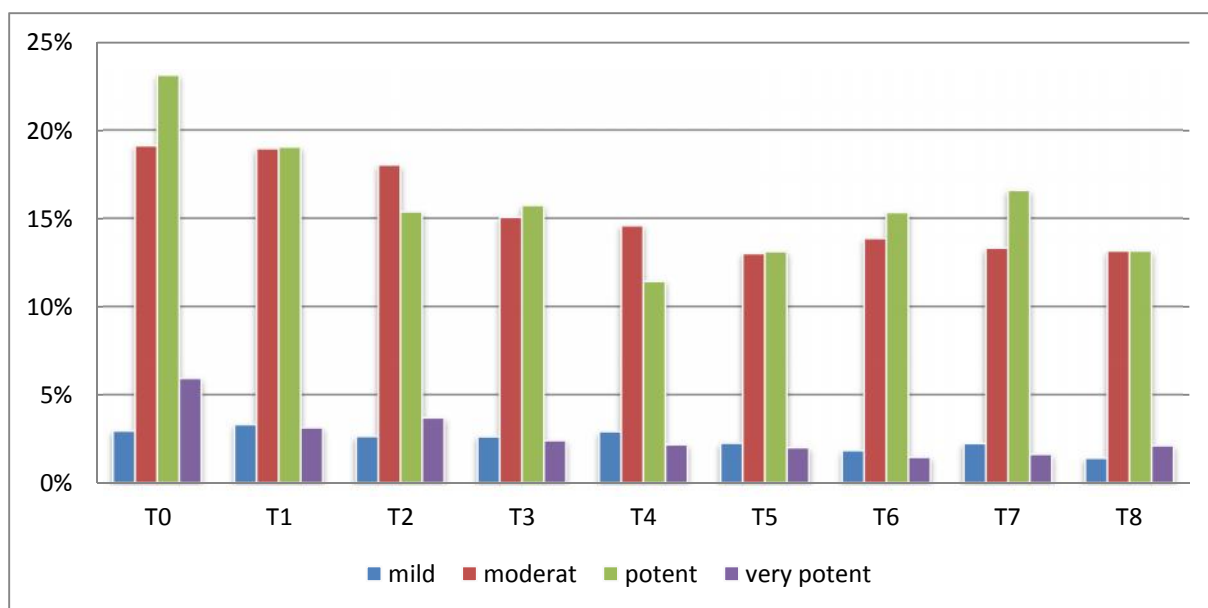


FIGURE S2A: TOPICAL CORTICOSTEROIDS PRESCRIBED AT EACH VISIT IN THE REGISTRY (IN %)

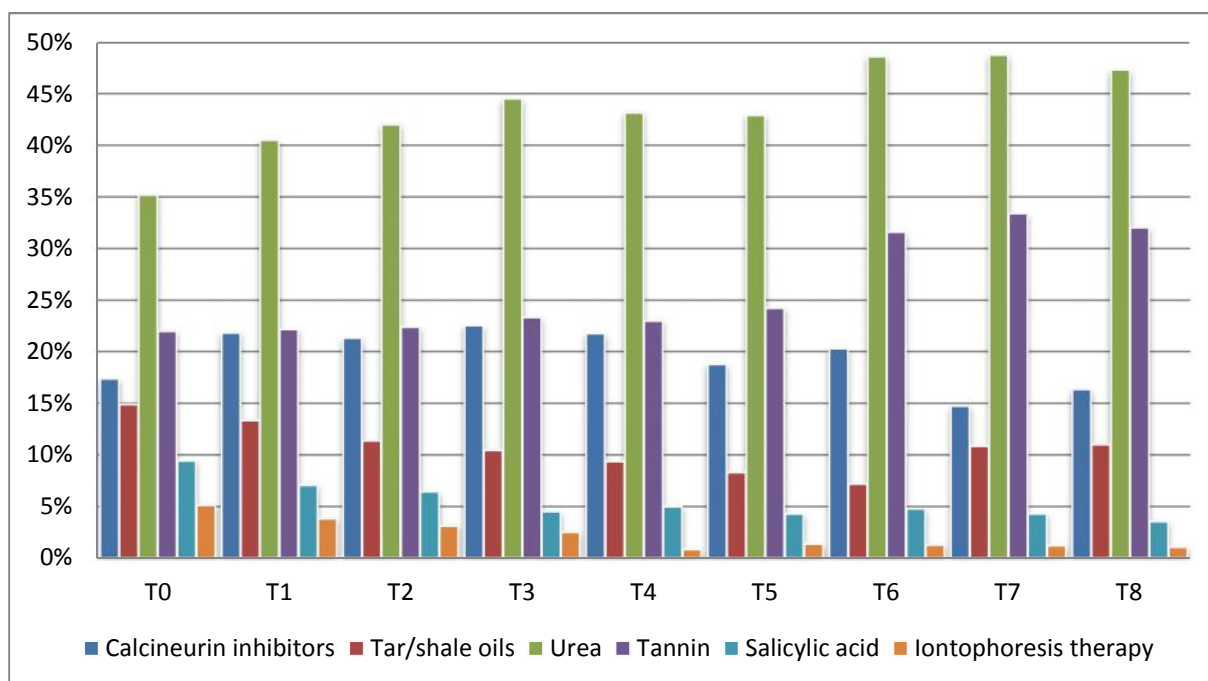


FIGURE S2B: TOPICAL THERAPY PRESCRIBED AT EACH VISIT IN THE REGISTRY (IN %)

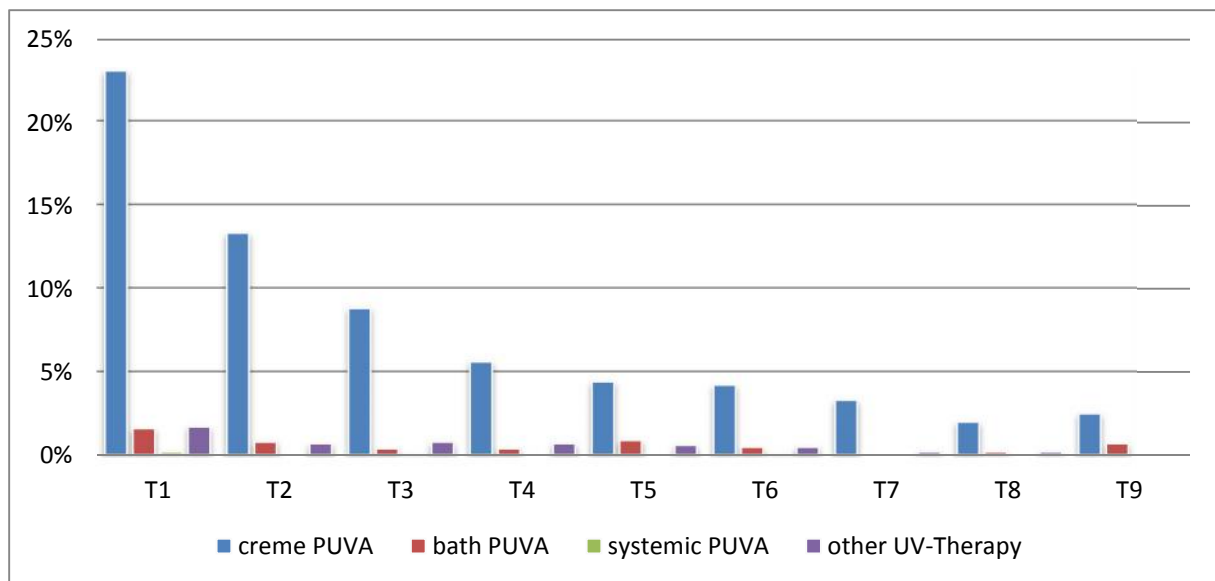


FIGURE S2C: UV THERAPY PRESCRIBED AT EACH VISIT IN THE REGISTRY (IN %)

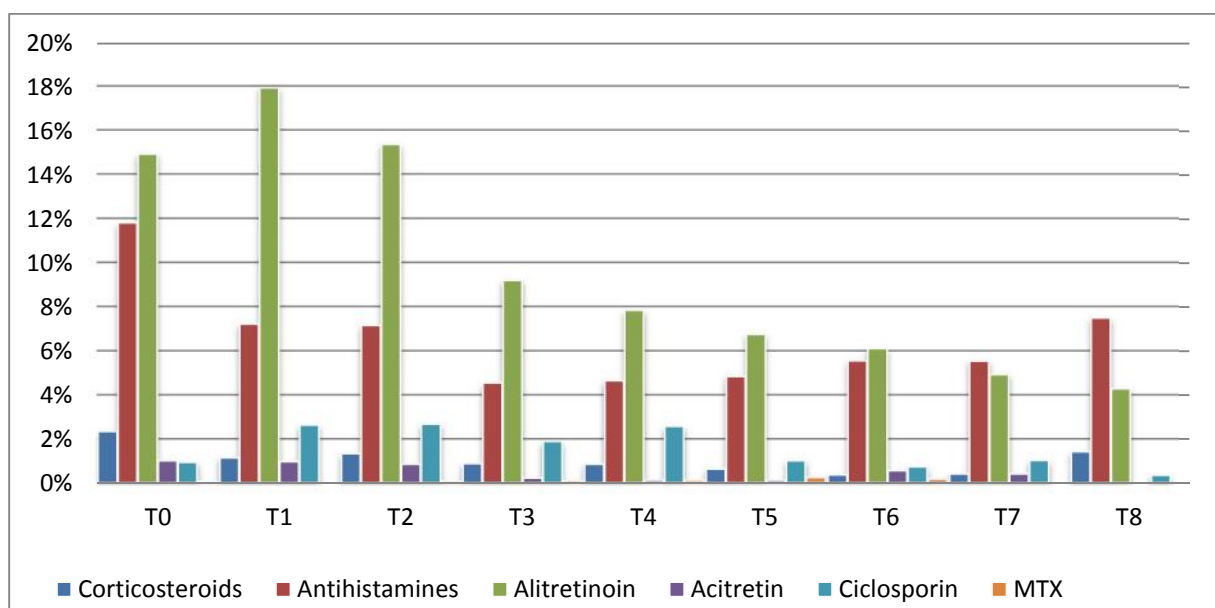


FIGURE S2D: SYSTEMIC THERAPY PRESCRIBED AT EACH VISIT IN THE REGISTRY (IN %)

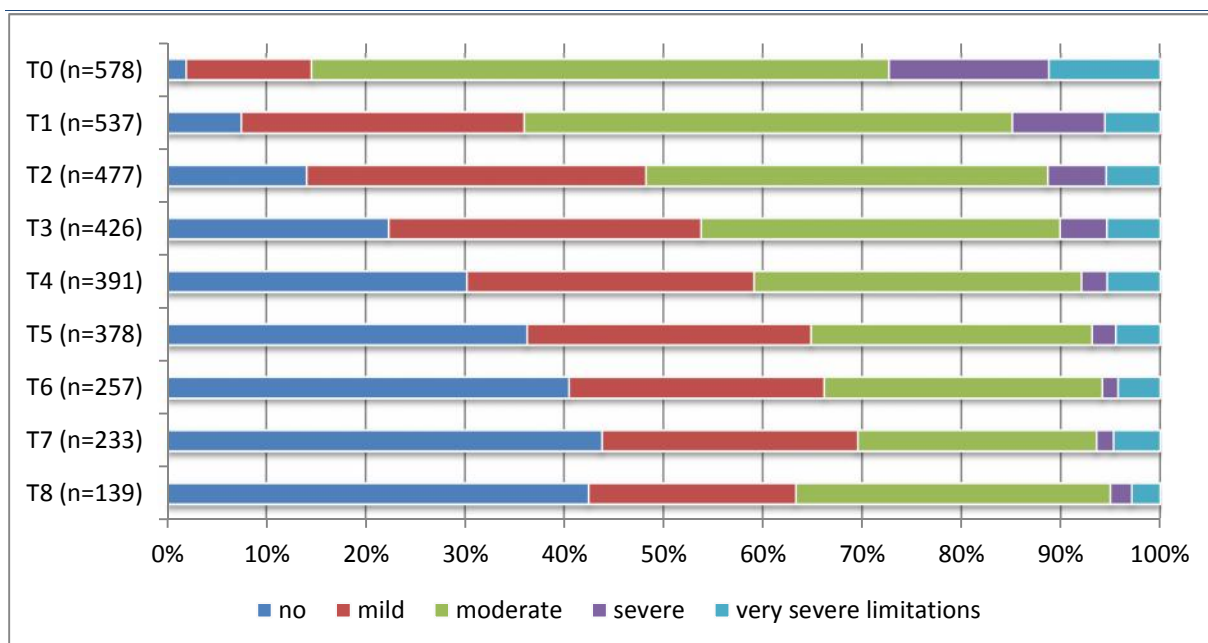


FIGURE S3A: CLINICAL ASSESSMENT OF DISEASE SEVERITY (ODDI)

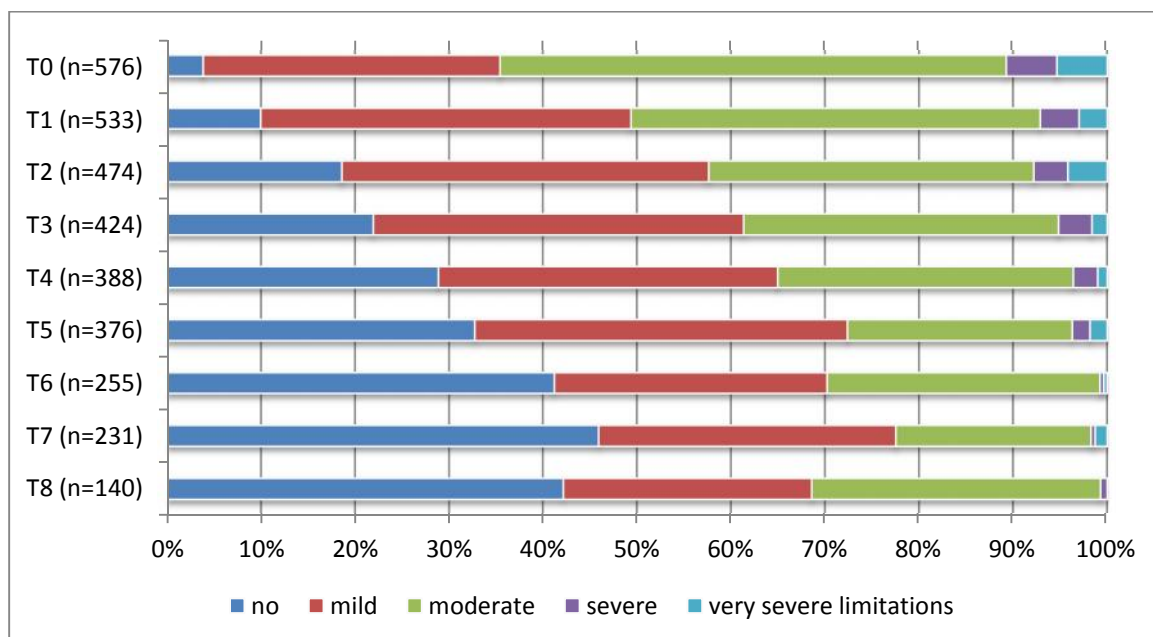


FIGURE S3B: ASSESSMENT OF WORK-RELATED ACTIVITIES (ODDI)

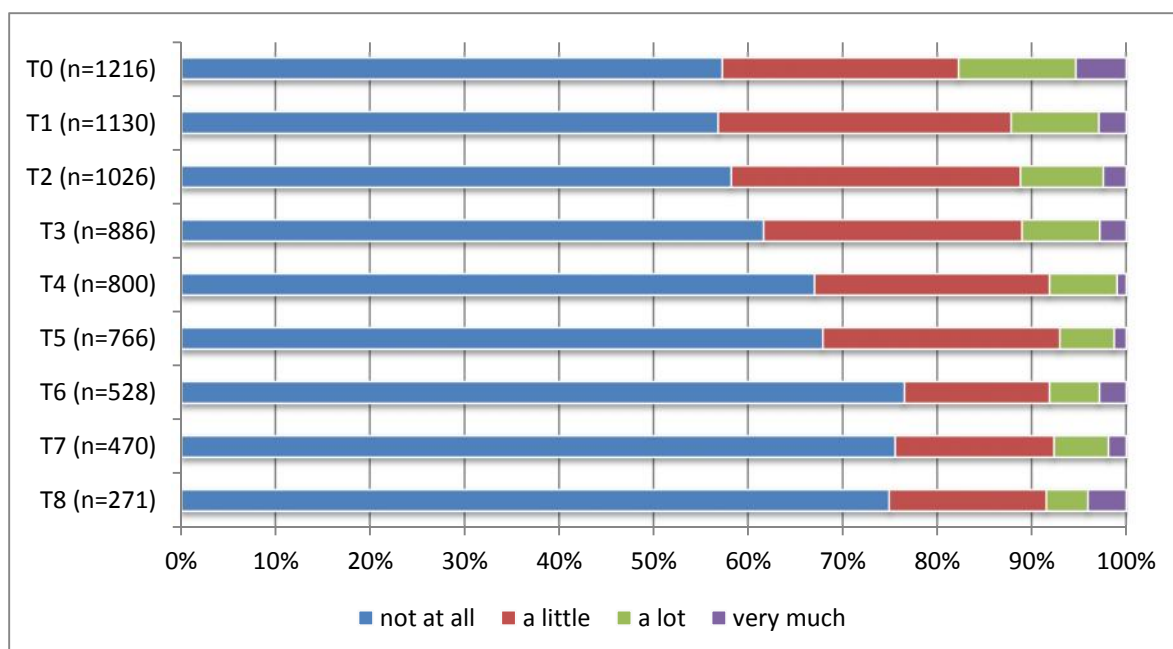


FIGURE S4A: SIDE EFFECTS OF TREATMENT AS REPORTED BY THE PATIENT

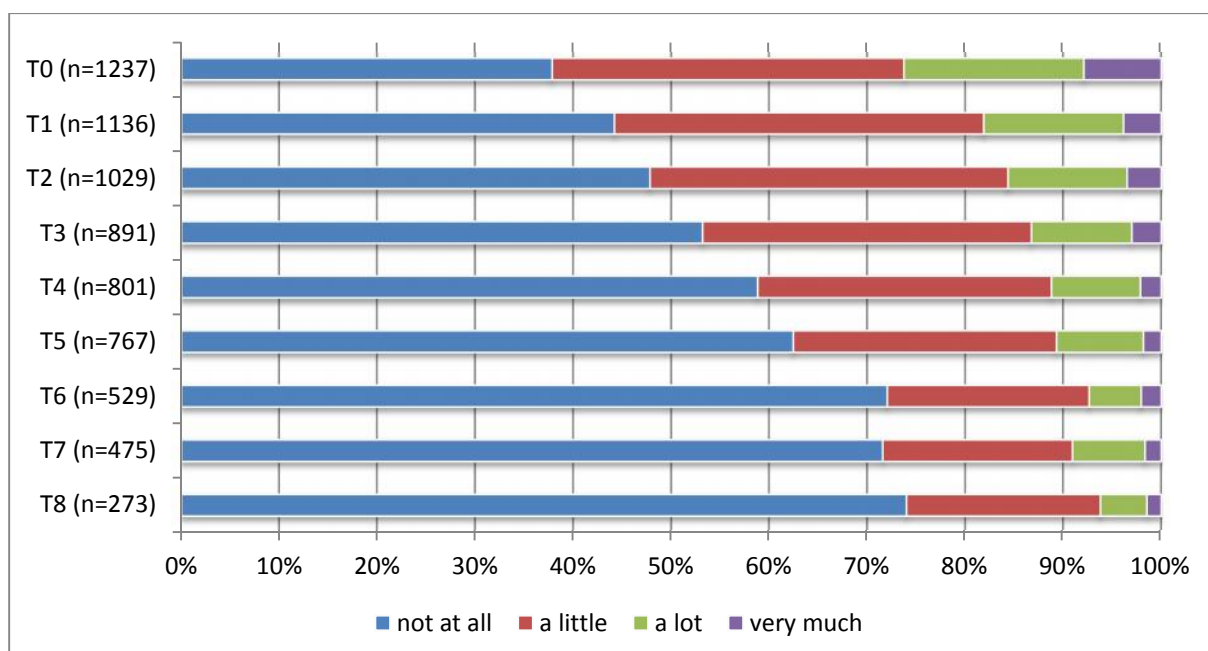


FIGURE S4B: 'TREATMENT IS TIME CONSUMING' AS REPORTED BY THE PATIENT

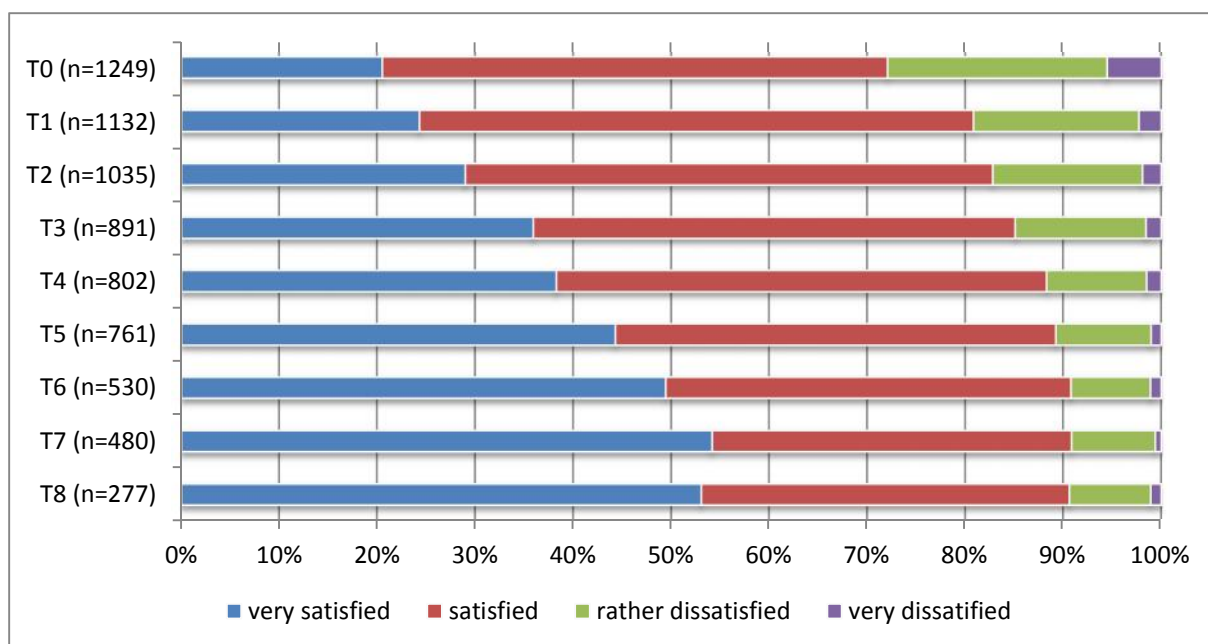


FIGURE S4C: TREATMENT SATISFACTION AS REPORTED BY THE PATIENT

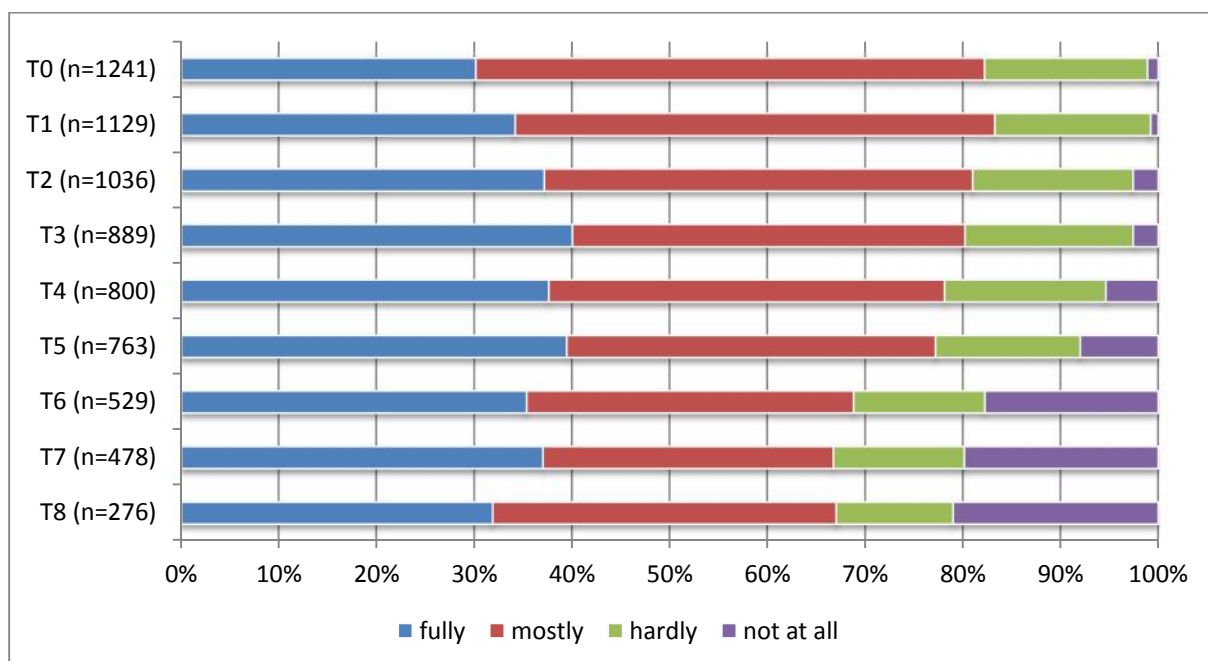


FIGURE S4D: ABILITY TO PERFORM TREATMENT RECOMMENDATIONS AS REPORTED BY THE PATIENT