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Intravenous vitamin C in the treatment of allergies: an interim subgroup analysis of a long-term observational study

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Abstract

Objective: Oxidative stress appears to be a key factor in the pathogenesis of allergic diseases and a potential therapeutic target in allergy treatment. Allergic diseases are reportedly associated with reduced plasma levels of ascorbate, which is a key physiological antioxidant. Ascorbate prevents excessive inflammation without reducing the defensive capacity of the immune system.

Methods: An interim analysis of a multicenter, prospective, observational study was conducted to investigate the change in disease-specific and nonspecific symptoms (fatigue, sleep disorders, depression, and lack of mental concentration) during adjuvant treatment with intravenous vitamin C (Pascorbin®; Pascoe, Giessen, Germany) in 71 patients with allergy-related respiratory or cutaneous indications.

Results: Between the start and end of treatment, the mean sum score of three disease-specific symptoms decreased significantly by 4.71 points and that of four nonspecific symptoms decreased significantly by 4.84 points. More than 50% of patients took no other allergy-related medication besides vitamin C.

Conclusions: Our observations suggest that treatment with intravenous high-dose vitamin C reduces allergy-related symptoms. Our observations form a basis for planning a randomized

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controlled clinical trial to obtain more definitive evidence of the clinical relevance of our findings. We also obtained evidence of ascorbate deficiency in allergy-related diseases.
Trial registration: Clinical Trials NCT02422901.

Keywords
Ascorbic acid, allergic rhinitis, allergic asthma, dermatitis, eczema, human, pruritus, intravenous administration

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Introduction

The management of allergic diseases represents a major health challenge for the 21st century. Complementary and alternative approaches are under investigation.[1–4] A recent review of the molecular redox mechanisms in asthma concluded that oxidative stress plays not only a key role in the pathophysiology of asthma but is also a promising therapeutic target.[5]

During the stages of acute allergic inflammation and in allergy-related respiratory or skin infections, the production of reactive oxygen species (ROS) by membrane-associated NADPH oxidase proteins of neutrophils, macrophages, or eosinophils[5–7] plays an important role.[7] Although ROS are physiologically produced to eliminate pathogens and invading microorganisms,[6] they represent a substantial force in individuals with allergy by promoting pro-inflammatory conditions.[8]

Interestingly, NADPH oxidase proteins are also of particular relevance in pollens and seem to provide a signal that augments antigen-induced allergic airway inflammation.[9] In addition, histamine production and release seems to be triggered by inflammation and ROS,[10] causing mast cell degranulation[11,12] and/or induction of histidine decarboxylase.[13]

Identifying ways to suppress the pro-inflammatory activity of ROS and limit potential damage to biological molecules seems to be of significant clinical relevance. A targeted antioxidant intervention to counteract pathophysiological increases in ROS can be achieved by increasing the body's low-molecular-weight antioxidants by dietary or pharmacological interventions.[14] Vitamin C (ascorbate) is one of the most effective aqueous-phase antioxidants in human blood plasma for protection against oxidative stress.[15–17] Elevating the plasma concentration of ascorbate, which can only be achieved by intravenous (iv) administration,[18] is a popular complementary treatment in the management of inflammatory conditions.[19,20]

We obtained data from the present multicenter, prospective, observational study to document the clinical effects of high-dose iv vitamin C in the treatment of patients with known respiratory or cutaneous allergies. We obtained findings that are novel to the best of our knowledge.

Materials and methods

This interim subgroup analysis of a long-term (November 2012 to October 2022) observational study was performed to document the use of Pascorbin® 7.5 g (authorized medicinal product containing 7.5 g ascorbate; Pascoe pharmazeutische Präparate GmbH, Giessen, Germany) in

patients with allergic diseases for the reduction of symptoms related to oxidative stress and vitamin C deficiency. Assessment of treatment dosages and treatment tolerance were further aims. To obtain data regarding changes in the application behavior for the investigated product, a 10-year period for submission of case report forms (CRFs) was chosen. All consecutive patients who received elective iv ascorbate treatment for an acute or chronic allergic condition (diagnosis of allergic diseases was previously confirmed and documented by the attending physician) from 1 November 2012 to 15 September 2014 were included in this study. The patients' characteristics and the criteria for data selection are shown in Figure 1 and Table 1, respectively. Vitamin C deficiency was diagnosed by laboratory tests or symptom investigation. The patients were informed of possible unwanted adverse effects and the anonymity of the data processing, which was assured by a signed statement. All patients signed a statement of agreement to use and publish their data for the observational study.

The study design and concept are based on the recommendations of the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM, German Federal Institute for Drugs and Medical Devices) and the Paul-Ehrlich-Institute in accordance with German laws and the principles of the Declaration of Helsinki and Good Clinical

Table 1. Eligibility criteria

Inclusion criteria
Age of >12 years
Treatment with vitamin C infusion (7.5 g) due to vitamin C deficiency
Patient's statement of agreement to use and publish their data for the observational study
Exclusion criteria (anamnestic)
Oxalate urolithiasis, nephrolithiasis
Renal insufficiency
Iron storage disease (thalassemia, hemochromatosis, sideroblastic anemia)
Erythrocytic glucose-6-phosphate dehydrogenase deficiency
Pregnancy and lactation
Hypersensitivity to an ingredient

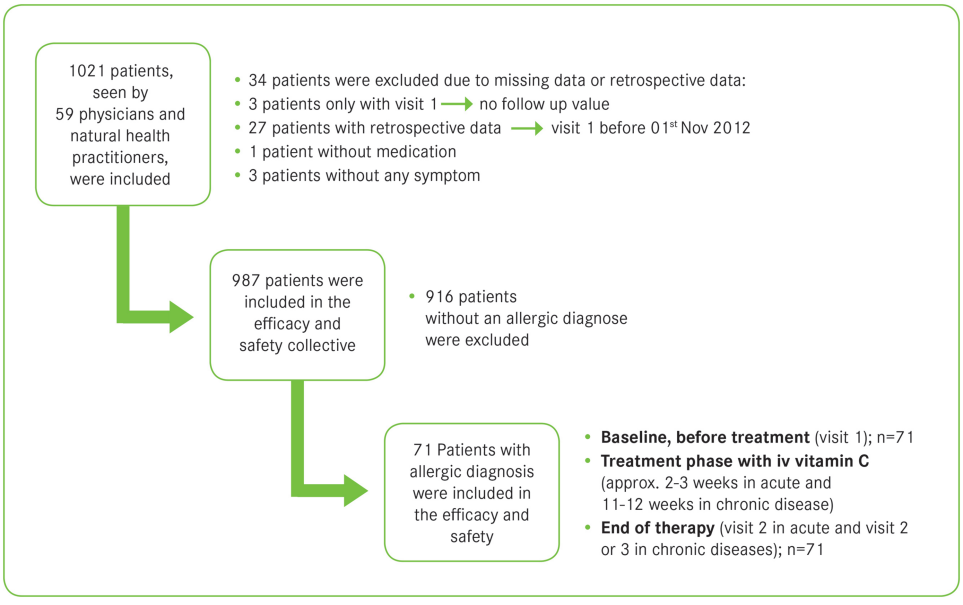

Figure 1. Flowchart of study patients.

Practice. The study was registered at the United States Clinical Trial registry (registration number: NCT02422901).

The participating physicians and natural health practitioners were informed about the scientific basis of this observational study and were requested to complete a detailed form indicating the patients' clinical characteristics, diagnosis, dosage, and disease symptoms for any elective use of iv vitamin C treatment. Depending on the duration and state of the disease, acute or chronic allergic diseases were differentiated by the physicians, and two separate CRFs were available. The treating physician used the CRF for acute disease if the symptomatology started within the previous 4 weeks and the patient was symptom-free prior to that time (e.g., allergic rhinoconjunctivitis after the start of the pollen season). The characteristics of patients with chronic disease were documented using a different CRF if recurrent symptomatology had been present for longer than the previous 4 weeks (several patients had allergic disease symptoms for several months, such as those with atopic eczema). Patients with psoriasis as the primary diagnosis were included in this interim subgroup analysis because concomitant allergic disease was often present. Furthermore, the symptoms are very similar because of the inflammatory character of the disease.

Data were collected before the start of vitamin C treatment (visit 1, baseline) and after the end of treatment in patients with acute disease (visit 2, approximately 2–3 weeks). In patients with chronic disease, data were collected after an interim observation at 6 to 8 weeks (visit 2) and after the end of treatment (10–14 weeks) (visit 3).

Each patient received iv vitamin C (Pascorbin® 7.5 g/50 mL) diluted in a suitable carrier solution such as 100 mL NaCl 0.9%. Because the vitamin C amount needed to treat a deficiency state depends on different parameters (such as the extent of the deficiency, body weight, age, glomerular filtration rate, and continued metabolic turnover due to oxidative stress), up to 7.5 g can be administered according to the summary of product characteristics. To avoid a shortage, the doctors participating in the study decided to use 7.5 g because vitamin C is consumed continuously due to oxidative stress produced by the allergic response and an excess is given during infusion to saturate tissue. This is a commonly used procedure because vitamin C is a well-tolerated substance that is not accumulated in the body but rapidly eliminated via the kidneys.

The use of other remedies was documented, primarily antiallergic reagents (antihistamines; topical, inhaled, or systemic corticosteroids; beta-2 sympathomimetics; parasympatholytics; and leukotriene receptor antagonists) and antibiotics.

Primary endpoints

The main study parameter was the response of symptoms (change in score) during the period of iv vitamin C treatment. Therefore, at the beginning (visit 1) and end (visit 2 for acute disease, visit 3 for chronic disease) of the observation period, the severity of each symptom was scored on a 4-point Likert scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe) by the treating physician or natural health practitioner.[21–23]

A one-sample t-test (two-sided, with $\alpha = 0.05$) was used to assess the changes between baseline and the final visit (calculated as post-treatment minus pretreatment). The statistical analyses were performed by an independent statistician. Subgroup analyses were carried out for the following categories:

- Type of disease
  - Acute
  - Chronic

- Diagnosis (International Classification of Diseases, 10th revision)
  - Diseases of the respiratory system (J00–J99)
  - Diseases of the skin and subcutaneous tissue (L00–L99)

The changes in the symptom scores were classified as improvement, no change, and deterioration of symptoms (as designated on the CRFs). In the symptom evaluation, only data of those patients who displayed the symptom and for whom pretreatment and post-treatment assessments were documented were included.

Disease-specific symptoms. The disease-specific symptoms were not predetermined. For each patient, up to three of the most prominent symptoms were assessed as free text and then assigned to appropriate categories (MedDRA coding, version 15.1 and higher) after data collection. For the 4-point Likert scale (0–3 points) of symptom severity, the range of possible sum scores was 0 to 9 points. The three most frequently documented symptoms in the study population were assessed in detail.

Nonspecific symptoms. Four nonspecific symptoms (fatigue, sleep disorders, depression, and lack of mental concentration) as assessed by means of the 4-point Likert scale (0–3 points) had a possible sum score ranging from 0 to 12 points.

Pain. Every type of pain (e.g., headache, abdominal, or cutaneous pain) was evaluated by means of a numeric rating scale for pain ranging from 0 (no pain) to 10 (extreme pain).[24]

Secondary outcome measures

Assessment of efficacy and tolerability of previous medication and of vitamin C. The efficacy of the previous/current therapies and vitamin C was judged by the physicians on a five-category scale:

- Very good efficacy (symptoms eliminated)
- Good efficacy (symptoms substantially improved)
- Moderate efficacy (symptoms slightly improved)
- No effect (symptoms unchanged)
- No effect (symptoms worsened)

The tolerability was judged on the basis of a two-category scale:

- Very well tolerated (no side effects)
- Poorly tolerated (side effects)

Ascorbate concentration. Serum ascorbate concentrations were measured before the start of vitamin C treatment (at visit 1). After collection, the serum samples were cooled, centrifuged, and mixed with a stabilization and precipitating reagent. They were then frozen for storage until analysis. Reversed-phase high-performance liquid chromatography (ProntoSIL C18 AQ, 5 μm; Bischoff Chromatography, Atlanta, GA, USA) was used to analyze the serum ascorbate levels. The intra-assay coefficients of variation were 5.6% (0.44 mg/dL) and 4.1% (1.8 mg/dL), and the inter-assay coefficients of variation were 8.8% and 5.9%.

Safety. Safety of the vitamin C treatment was assessed by the attending physician in terms of adverse events and possible relatedness of such events to vitamin C treatment, underlying disease, or co-medication.

Results

In total, 71 patients with a mean age ± standard deviation of 43.14 ± 17.86 years and an almost even sex distribution were identified using the inclusion criteria for previously confirmed allergic respiratory disease

(56.3%) or allergic cutaneous disease (43.7%) (Table 2). The frequency of different types of allergic diseases and the duration of acute and chronic diseases are documented in Table 2. Endocrine, nutritional, and metabolic diseases were the most frequently reported concomitant diseases (E00–E90; n = 8), followed by diseases of the digestive system (K00–K93; n = 7) and diseases of the circulatory system (I00–I99; n = 5) and respiratory system (J00–J99; n = 5).

Table 2. Baseline demographic and clinical characteristics of patients (n = 71)

Age, years	43.14 ± 17.86, (12–79)
Sex	
Male	38 (53.5%)
Female	33 (46.5%)
Body mass index, kg/m^2	24.95 ± 3.61, (18.4–33.6)
Inclusion diagnosis (ICD-10 category)	
J00–J99: Diseases of the respiratory system	40 (56.3%)
J30: Vasomotor and allergic rhinitis	30 (75.0%)
J45: Bronchial asthma	10 (25.0%)
L00–L99: Diseases of the skin and subcutis	31 (43.7%)
L20–L30: Dermatitis and eczema	19 (61.3%)
L40–L41 Psoriasis and parapsoriasis	7 (22.6%)
L50: Urticaria	5 (16.1%)
Proportion of acute and chronic diseases	
Respiratory allergic disease (acute)	26 (65.0%)
Respiratory allergic disease (chronic)	14 (35.0%)
Cutaneous allergic disease (acute)	11 (35.5%)
Cutaneous allergic disease (chronic)	20 (64.5%)
Concomitant disease	
Yes	24 (33.8%)
No	47 (66.2%)
Duration of inclusion diagnosis, years	
Acute	0.07 ± 0.13
Chronic	19.23 ± 18.92
Intake of antiallergic reagents	
Yes	25 (35.2%)
No	46 (64.8%)
Intake of antibiotics	
Yes	11 (15.5%)
No	60 (84.5%)
Number of antiallergic reagents or antibiotics	
1	21 (61.8%)
2	7 (20.6%)
3	4 (11.8%)
≥4	2 (5.9%)

Data are presented as mean ± standard deviation, range, or n (%).
ICD-10: International Classification of Diseases, 10th revision.

Of patients included in the interim subgroup analysis, 45.1% (32/71) received additional treatment with antiallergic reagents or antibiotics (Table 2).

Disease-specific symptoms

Two patients (both with psoriasis) had no disease-specific symptoms throughout the observation period; they were therefore excluded from the analysis. Thus, 69 patients were included in the analysis and had a total of 182 symptoms (average of 2.6 symptoms/patient), corresponding to 52 preferred terms (MedDRA coding, version 15.1 and higher). The three most frequently preferred terms were pruritus (n = 31), rhinitis (n = 26), and restlessness (n = 15). During the observation period, symptoms improved in 67 (97.1%) of the 69 analyzed patients, and 173 (95.1%) of the 182 recorded disease-specific symptoms improved. The mean sum score of the disease-specific clinical symptoms decreased significantly from 5.91 at baseline to 1.20 at the final visit (mean change, −4.71, $p < 0.0001$). Subgroup analyses revealed significant changes for each diagnosis (respiratory or cutaneous) and for acute and chronic disease ($p < 0.0001$) (Table 3).

Analysis of the most frequently recorded symptoms revealed symptom improvement rates (in terms of the number of patients) during the observation period of 29/31 (93.5%), 25/26 (96.2%), and 15/15 (100%) for pruritus, rhinitis, and restlessness, respectively (Table 4).

The fraction of symptom-free patients and patients with only mild symptoms at the end of the observation period was 29/31 (93.6%) for pruritus, 23/26 (88.5%) for rhinitis, and 12/15 (80.0%) for restlessness at the end of the observation (Figure 2).

Table 3. Sum scores (0–9 points) for specific symptoms (n = 69)

Total population and subgroups	Start of treatment	End of treatment	Change (beginning – end)	Probability estimate*
Total population	5.91	1.20	4.71	$p < 0.0001$
Respiratory allergic diseases	5.58	1.08	4.50	$p < 0.0001$
Cutaneous allergic diseases	6.38	1.38	5.00	$p < 0.0001$
Acute diseases	5.78	1.46	4.32	$p < 0.0001$
Chronic diseases	6.06	0.91	5.16	$p < 0.0001$

*Student's t-test.

Table 4. Changes in the three most frequently recorded disease-specific symptoms, baseline/visit 1 *vs.* end of observation period

	Pruritus		Rhinitis		Restlessness	
	n	%*	n	%*	n	%*
Improvement	29	93.5	25	96.2	15	100.0
No change	2	6.5	1	3.8	0	0.0
Deterioration	0	0.0	0	0.0	0	0.0
Valid data	31	100.0	26	100.0	15	100.0
Missing data	38	–	43	–	54	–

*Valid data analysis; missing data refer to patients without the symptom because the treating physician selected for each patient the three most prominent symptoms among all allergic symptoms.

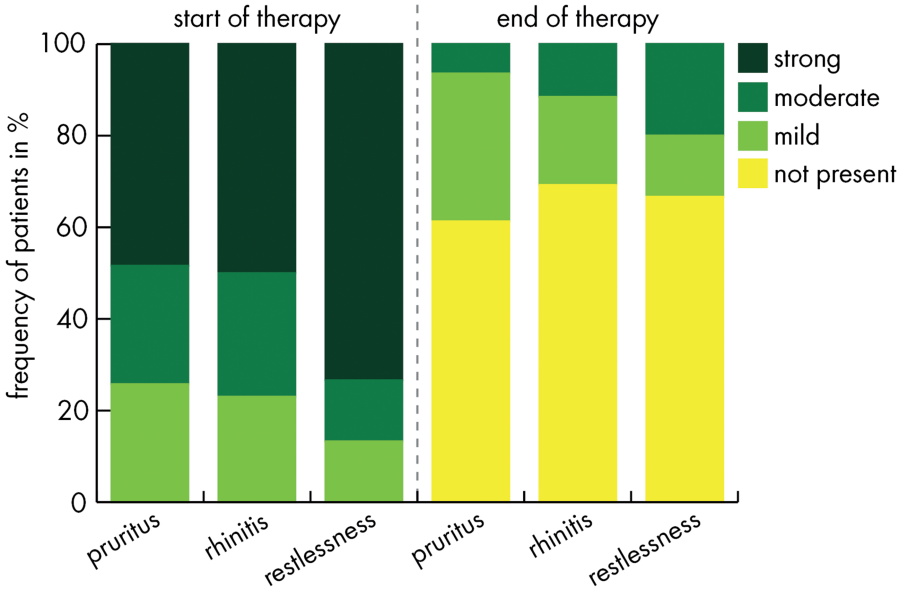

Figure 2. Frequencies of the three most frequently recorded disease-specific symptoms. The severity of each symptom was documented on a 4-point Likert scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe) by the treating physician or natural health practitioner at start and end of treatment. Valid data for pruritus, n = 31; for rhinitis, n = 26; and for restlessness, n = 15.

Regarding the percentage of patients with an improvement in the symptom sum score, there was a tendency for greater improvement in the patients receiving no antiallergic and/or antibiotic medication additionally to vitamin C (93.8% vs. 100%).

Nonspecific symptoms

In total, nonspecific symptoms (fatigue, sleep disorders, depression, and lack of mental concentration) were analyzed in 70 patients because 1 patient had no nonspecific symptoms. The mean sum score of nonspecific clinical symptoms decreased from 5.93 at baseline to 1.09 at the final visit (mean change, −4.84; $p < 0.0001$). Subgroup analyses revealed significant changes for each diagnosis (respiratory or cutaneous) and for acute and chronic disease ($p < 0.0001$) (Table 5).

Nonspecific symptoms were found to decrease in 65 (92.9%) of 70 of patients during the observation period. The fraction of symptom-free patients and patients with only mild symptoms at the end of the observation was >90% for all nonspecific symptoms. The degrees of improvement of individual symptoms are presented in Table 6.

The frequencies of the nonspecific symptoms, according to the degree of manifestation, are shown in Figure 3.

Regarding the percentage of patients with an improved sum score, there was a tendency for greater improvement in the patients receiving no antiallergic and/or antibiotic medication additionally to vitamin C (90.3% vs. 94.9%).

Any type of associated pain

Of the 70 analyzed patients, 48 (68.6%) experienced pain of some type. The initial mean value of 3.8 ± 2.8 on the numeric rating scale decreased to 0.7 ± 1.3 after treatment.

Table 5. Sum scores (0–12 points) for nonspecific symptoms (fatigue, sleep disorders, depression, and lack of concentration) (n = 70)

Total population and subgroups	Start of treatment	End of treatment	Change (beginning – end)	Probability estimate*
Total population	5.93	1.09	4.84	$p < 0.0001$
Respiratory allergic diseases	5.10	1.10	4.00	$p < 0.0001$
Cutaneous allergic diseases	6.97	1.06	5.90	$p < 0.0001$
Acute diseases	4.97	1.35	3.62	$p < 0.0001$
Chronic diseases	7.00	0.79	6.21	$p < 0.0001$

*Student's t-test.

Table 6. Changes in nonspecific symptoms, baseline/visit 1 *vs.* end of observation period

	Tiredness/ fatigue		Sleep disorders		Depression		Lack of concentration	
	n	%*	n	%*	n	%*	n	%*
Improvement	58	93.5	49	92.5	42	95.5	55	91.7
No change	3	4.8	4	7.5	2	4.5	4	6.7
Deterioration	1	1.6	0	0.0	0	0.0	1	1.7
Valid data	62	100.0	53	100.0	44	100.0	60	100.0
Missing data	8	–	17	–	26	–	10	–

*Valid data analysis; missing data refer to patients without the symptom at the beginning of treatment.

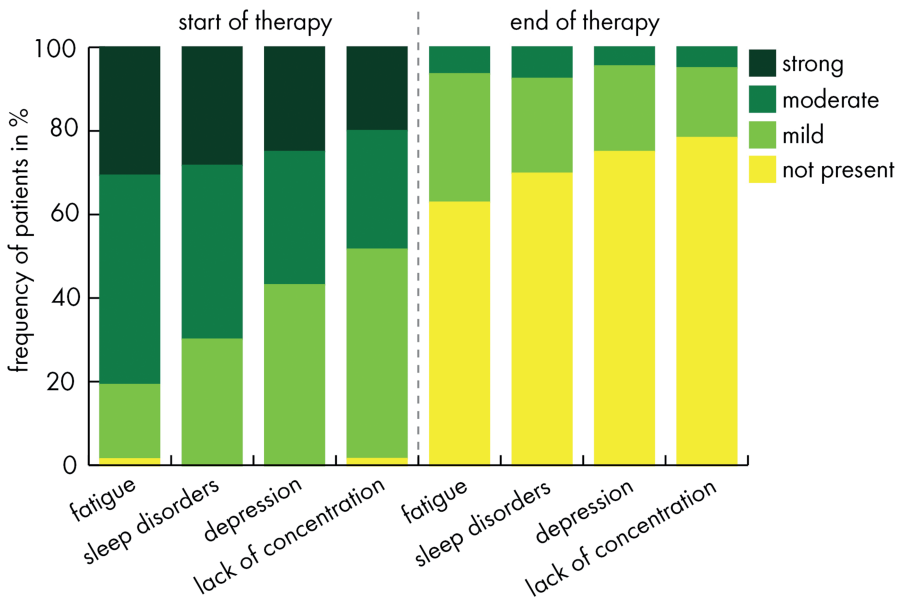

Figure 3. Frequency of nonspecific symptoms (tiredness/fatigue, sleep disorders, depression, and lack of mental concentration). The severity of each symptom was documented on a 4-point Likert scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe) by the treating physician or natural health practitioner at start and end of treatment. Valid data for tiredness/fatigue, n = 62; for sleep disorders, n = 53; for depression, n = 44; and for lack of mental concentration, n = 60.

Duration and dosage of vitamin C

Treatment was performed during a mean of 3.2 weeks for acute disease and 11.9 weeks for chronic disease. The mean number of vitamin C infusions was 7 in the acute disease group and 26 in the chronic disease group. Because the vitamin C infusion was administered mainly over the complete treatment period, the frequency of infusions was two to three per week for both acute and chronic states.

Subgroup analysis of serum ascorbate concentrations

Serum ascorbate concentrations were measured in 21 of 71 patients (30%) prior to high-dose vitamin C treatment. The reason for this elective measurement lies in the fact that ascorbate measurements are not part of standard clinical laboratory assessments, and the costs of analysis are not reimbursable in Germany. Clinical vitamin C deficiency (scurvy) is defined as a plasma concentration of <0.2 mg/dL, and subclinical deficiency is defined as a plasma concentration of <0.5 mg/dL.[25,26] The latter vitamin C depletion applied to 15 of 21 (71.4%) of the analyzed patients. The mean serum ascorbate level was 0.34 mg/dL with a median of 0.2 mg/dL (Table 7).

Table 7. Vitamin C serum levels at baseline before treatment with Pascorbin®

Subgroups	Vitamin C (mg/dL)
Total (n = 21)	0.34 ± 0.28
Acute diseases (n = 13)	0.40 ± 0.31
Chronic diseases (n = 8)	0.24 ± 0.19
Respiratory diseases (n = 10)	0.45 ± 0.34
Cutaneous diseases (n = 11)	0.24 ± 0.17

Data are presented as mean ± standard deviation. Clinical vitamin-C-deficiency (ascorbate), <0.2 mg/dL; subclinical deficiency, <0.5 mg/dL.

Efficacy and tolerability of prior medication and vitamin C treatment

Of the 71 investigated patients, 51 (71.8%) reported the use of antiallergic medication before the start of vitamin C treatment. Assessment of the efficacy and tolerability of prior medication versus vitamin C is documented in Table 8. Notably, at the end of the observation period, 69% of the patients (n = 49) (data not shown) treated with vitamin C were assessed as having very good treatment efficacy (completely eliminated symptoms). In all cases, the physician recommended vitamin C treatment.

Table 8. Comparison of subjectively reported efficacy and tolerability of vitamin C *vs.* previous medication

	Previous therapy		Vitamin C	
Rating	n	%*	n	%*
Efficacy				
Very good and good efficacy	12	23.5	67	94.4
Moderate or no effect or deterioration	39	76.5	4	5.6
Tolerability				
Good tolerability	24	47.1	70	98.6
Poor tolerability	27	52.9	1	1.4
Total	51	100.0	71	100.0

*Valid data analysis.

Safety of vitamin C infusion

Very good tolerability was reported in 70 of 71 patients (98.6%). In 1 of the 71 patients (1.4%), 2 adverse reactions to vitamin C infusion were recorded, but treatment was continued. These adverse reactions were "repeated unpleasant sensation of cold a few hours after infusion" and "tiredness the next morning."

Discussion

The results of this interim subgroup analysis of a large observational study indicate that high-dosage vitamin C reduces disease-specific and nonspecific symptoms in patients with respiratory and cutaneous allergic conditions as evidenced by improvements in a standardized symptom score and the physicians' rating. The reduction in the sum scores of disease-specific and nonspecific symptoms was significant for the whole population and in the subgroup analyses of the type of diagnosis (respiratory or cutaneous) and disease (acute or chronic) ($p < 0.0001$).

This was an observational study without a control group; notably, however, 54% of our vitamin C-treated patients took no other allergy-related medication (antiallergic reagents or antibiotics). Comparison of the percentage of patients with an improvement in the symptom sum score showed no meaningful difference between patients with and without allergy-related medication besides vitamin C.

Interestingly, in this context, a randomized study showed corticosteroid-sparing effects of daily oral vitamin C substitution (1 g) in asthmatic patients.[27]

Despite symptomatic medication, diseases such as allergic rhinitis, asthma, and dermatitis are associated with impairments of functioning in day-to-day life and so reduce patients' health-related quality of life.[28] Therefore, in the treatment of allergic diseases, nonspecific symptoms such as fatigue, sleep disturbances, cognitive impairment, and mood changes are considered to warrant more attention than they have been given to date.[29,30] Our cohort data revealed fatigue in 88.6%, lack of concentration in 85.7%, sleep disorders in 75.7%, and depression in 62.9% of the study group at the start of treatment.

Notably, we observed that iv vitamin C had a greater effect on chronic nonspecific symptoms than on acute nonspecific symptoms, with a nearly 100% greater sum score reduction (6.21 vs. 3.62) (see Table 5). These symptoms may be either related to inflammation and oxidative stress or associated with the undesired effects of antihistaminic drugs.

Sleep impairment, which improved in 92.5% of affected patients in our study group, had a demonstrably significant impact on health-related quality of life in patients with allergic rhinitis and atopic dermatitis.[31,32]

The observed reduction of specific symptoms, such as rhinitis and pruritus, in our study group may have been associated with the histamine-reducing effect of vitamin C, which was examined in other studies. The effect of vitamin C on histamine blood levels has been investigated in both preclinical[33–36] and clinical studies,[37–42] but the detailed mode of action has not been fully elucidated. In a recent study investigating the acute effect of 7.5 g of iv vitamin C on the histamine levels in 89 patients with allergies or upper respiratory infections, a significant reduction in the histamine levels was observed. A higher initial serum histamine level was associated with a more pronounced observed reduction after vitamin C treatment.[41] Regulation and modulation of histamine levels by vitamin C appear to be biological phenomena because a similar relationship was reported in guinea pigs, who, like humans, cannot synthesize ascorbate.[43] In animals that synthesize vitamin C on demand, histaminosis

is accompanied by a rise in circulating ascorbate.[44] Several investigations have shown a correlation between ascorbate depletion and histaminaemia.[40] Histamine levels increased exponentially as plasma ascorbate decreased to <1 mg/dL, and a further reduction to <0.7 mg/dL resulted in a highly significant increase in the blood histamine level.[40] Although serum ascorbate levels were only available in an elective subgroup of 21 patients (29.6%) in the present interim analysis, a severe deficiency (median, 2.0 mg/dL) was very apparent, and 18 of the 21 investigated patients (85.7%) had plasma ascorbate levels below the critical value of 0.7 mg/dL. This corresponds well to the observed improvements in this patient cohort, in which the sum score for specific symptoms improved in all 18 patients and the score for nonspecific symptoms improved in 17 of 18 patients.

Therefore, an important therapeutic goal may be to prevent ascorbate levels declining to <0.7 mg/dL in patients with allergic diseases. However, the optimal plasma ascorbate levels for allergic individuals remain undefined.

The observed extent of pain reduction (81.6%) was similar to that of symptom reduction. Because inflammation and oxidative stress play a significant pathophysiological role in the development of pain, vitamin C was recently considered an important component of pain treatment.[45,46] In patients with herpes zoster, cancer and postoperative states, iv vitamin C was shown to reduce or prevent pain.[21,47–49]

Although serum ascorbate levels were only available in an elective subgroup of less than one-third of the cohort, the observed severe baseline deficiency is consistent with findings in patients with other inflammatory diseases.[50–54] Ascorbate is an important low-molecular-weight antioxidant that maintains antioxidative defenses at the air–lung interface.[55] Any loss of ascorbate across the large surface area of the lung induces a major drain on the systemic ascorbate reserves; this has already been documented in patients with asthma,[50,56–58] but not in patients with all other allergic diseases. However, patients with atopic dermatitis and psoriasis reportedly have reduced cutaneous ascorbate levels.[59,60] In our subgroup of patients who underwent elective ascorbate measurements, respiratory diseases (n = 10) and cutaneous diseases (n = 11) were evenly distributed. Both groups were found to have deficient serum ascorbate levels at baseline, but the levels in patients with cutaneous diseases (mean, 0.24 mg/dL) were much lower than those in patients with respiratory diseases (mean, 0.45 mg/dL). To the best of our knowledge, this finding provides novel preliminary evidence of the risk of ascorbate deficiency in patients with allergic diseases. The mean serum ascorbate levels appeared to differ between patients with acute and chronic (0.40 vs. 0.24 mg/dL) symptoms at baseline, with possibly lower levels associated with chronic disease.

The iv vitamin C treatment in this study was judged by the attending physician to be very safe and to have a higher tolerability than the prior medications, which were mainly antihistamines and local or systemic steroids. In our cohort, 52.9% of patients exhibited poor tolerability to standard allergy medication (Table 8) compared with only 1 of 71 patients who had an adverse event after iv vitamin C. This single patient developed adverse events during iv vitamin C but decided to continue receiving treatment. These observations are consistent with the findings of clinical studies and of a comprehensive survey that indicated the tolerability of iv vitamin C in doses up to 0.5 g/kg body weight (also up to 1.5 g/kg in phase-I trials) in patients without the documented contraindications of oxalate calculi, renal failure, hemochromatosis, and glucose-6-phosphate dehydrogenase deficiency.[19,61–63]

The observations from this noninterventional study form a basis for planning a randomized controlled clinical trial to obtain more definitive evidence of the clinical relevance of our findings. Based on the information received, an investigation of the effects of a 3-week intervention involving two to three infusions per week appears to be appropriate for patients with acute allergic diseases. In any case, nonspecific symptoms such as fatigue and lack of concentration should be inquired in addition to the allergy-specific symptoms.

Strengths and weakness of the study

We consider that our study provides important novel evidence suggesting that elective high-dose parenteral (iv) vitamin C treatment has positive effects on the progression of both disease-specific and nonspecific symptoms in patients with allergic diseases while exhibiting high tolerability in this patient group. Our observed effects on nonspecific symptoms, such as tiredness/fatigue, sleep disorders, lack of concentration, and depression, are important because these symptoms of quality of life are rarely monitored in detail in studies of patients with allergic diseases. Interpretation of our observations is significantly limited by the absence of a control group and the small sample of our interim subgroup analysis.

Conclusion

Preclinical and clinical data indicate that the reduction of oxidative stress and inflammation by vitamin C can be beneficial in patients with allergic diseases. This study provides observational evidence of the use of high-dose iv vitamin C in daily practice in the treatment of respiratory and cutaneous allergic diseases. We also observed evidence of serum ascorbate deficiency in our patients with allergic disease. Based on our observations and the plausible therapeutic effect of vitamin C, clinical trials with high-dose iv vitamin C are warranted in patients with allergic diseases.

Authors' contributions

CV conceived and initiated the study and participated in its design, contributed to the data evaluation, and drafted the manuscript. MR participated in the data evaluation and manuscript writing. BK participated in the data evaluation. KK participated in the study design and manuscript writing. AH participated in the study design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript. The explorative statistical analyses were performed by an independent statistician (Gesellschaft für Therapieforschung mbH, www.gkm-therapieforschung.de, Munich, Germany).

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Declaration of conflicting interest

AH, MR, and KK declare that they have no competing interests. CV and BK are employed by Pascoe pharmazeutische Präparate GmbH (Giessen, Germany).

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