
Effect of high-dose intravenous immunoglobulin treatment in therapy-resistant chronic spontaneous urticaria

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Background: Chronic spontaneous urticaria (CSU) lasting more than 6 weeks is one of the most disabling types of urticaria and often results in severely impaired quality of life. Patients with CSU are often unsatisfied with the standard treatment. Another treatment option recommended for patients with so-called nonresponding CSU according to the newest guidelines is intravenous immunoglobulin (IVIG).

Objective: To assess the efficacy and safety of high-dose IVIG as a treatment option in patients with therapy-resistant CSU.

Methods: Six patients with severe CSU unresponsive to other treatment options according to the newest guidelines for several weeks were treated with high-dose IVIG (2 g/kg every 4-6 weeks). The response to treatment was observed on the basis of clinical signs and reduction of co-medications using a special treatment score. Patients were studied during the treatment period and were followed up for an average of 16 months. Adverse events were assessed.

Results: Patients showed an improvement in symptoms and a reduction in co-medication use just after the first cycle. Symptoms such as itching, wheals, and edema were reduced after the first or second cycle of IVIG treatment. Four of 6 patients had complete remission after 2 to 4 cycles. One patient needed a longer continuation of treatment to reach a stable state of improvement, and another patient had a slight relapse after the seventh cycle. Adverse effects, such as headache and increased blood pressure, were observed only at the beginning of treatment.

Conclusion: High-dose IVIG represents an important therapeutic option in patients with severe CSU.

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INTRODUCTION

Urticaria is a common disease characterized by recurrent itching and wheals often accompanied by angioedema. Each wheal lasts for up to 1 day, angioedema sometimes 2 to 3 days. Urticaria overall occurs frequently, and nearly 1 in 4 persons experiences urticaria at some point in life. There are different subtypes of urticaria, eg, physical, chronic spontaneous, and acute urticaria. Chronic spontaneous urticaria (CSU) lasting for more than 6 weeks is one of the most disabling types of urticaria and frequently results in severely impaired quality of life, above all due to the pronounced itching (pruritus).¹ Identification of the various underlying causes or triggering factors in patients with CSU presents a challenge.

Generally, patients with severe CSU are often unsatisfied with the standard treatment of nonsedating antihistamines in single or increased dosages (up to 4-fold) combined with leukotriene antagonists. If symptoms still persist, immunomodulating therapies, such as cyclosporine and dapsone, are recommended. Another treatment option recommended for

patients with so-called nonresponding CSU according to the newest guidelines is intravenous immunoglobulin (IVIG), as stated by Zuberbier et al.²

As was first shown by O'Donnell et al,³ IVIG is a new treatment option that can induce prolonged remission in patients with severe and therapy-resistant CSU. The new guidelines for urticaria mention this treatment option as a further therapeutic possibility in therapy-resistant patients, paying attention to the unfavorable adverse effects of corticosteroids and other immunotherapeutic agents.²

First mentioned for the treatment of chronic thrombocytopenic purpura in childhood,⁴ IVIG has been applied most commonly for Guillain-Barré syndrome and other neuromuscular diseases. It is a polyvalent antibody product derived from the pooled plasma of healthy donors. Among inactivating autoreactive T cells, immunoglobulins restore the balance of anti-inflammatory T_H2 cytokines by containing antibodies to T_H1 cytokines. Furthermore, IVIG can downregulate B-cell production of antibodies by neutralizing pathogenic antibodies and can interrupt several steps in the complement cascade. Concerning the effect on hematopoietic cells, such as macrophages, dendritic cells, and neutrophils, IVIG can block Fcε receptor-mediated activity,⁵ which is considerable for patients with autoantibodies against IgE or Fcε receptor in their blood.

O'Donnell and coworkers³ treated 10 patients with positive autologous intradermal serum skin test (ASST) results and anti-FcεR1 autoantibodies not responsive to conventional

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treatment with 0.4 g/kg/d for 5 days. Clinical improvement was observed in 9 of 10 patients. These results, and our previous experience with patients with nonsufficiently treated CSU, prompted us to investigate this treatment option in more detail.

METHODS

Study Design and Patients

At the Department of Dermatology of the Universitätsmedizin Mainz, we performed a retrospective analysis of the efficacy and safety of IVIG therapy in 6 white patients (3 males and 3 females). All the patients were informed about the study and were asked whether they would like to participate; oral informed consent was given by all the patients. We did not seek ethical committee approval for this study because it does not report on primary research. All the data analyzed were collected as part of routine diagnosis and treatment procedures of CSU at the Department of Dermatology.

The mean patient age was 47 years (range, 16-72 years). All the patients had severe CSU accompanied by episodic angioedema poorly or not responding to treatment according to international guidelines.² The mean duration of disease was 5.2 years (range, 1-11 years). All the patients had recurrent severe episodes of urticaria with a need for high doses of corticosteroids and were restricted in their daily life. Several immunosuppressive therapies, such as cortisone, dapsone, and cyclosporine, as add-on therapy either were ineffective or were impossible to administer due to contraindications or adverse effects, so we decided to start IVIG treatment after confirming that the health insurance company would pay for the treatment.

Patients were treated with IVIG (Biotest, Dreieich, Germany), 2 g/kg body weight over 2 days in periods of 4 to 6 weeks. Every treatment dose was split into 2 identical infusions given during approximately 6 hours; the total number of cycles ranged from 3 to 11, depending on the response of the patient and on the individual insurance coverage of the patient. The insurance providers of the patients were quite different in allowing the costs; that is why we had to stop treatment in 2 patients immediately after they responded, whereas in another patient, with agreement from the insurance provider, we were allowed to continue the treatment for 6 additional cycles to stabilize his condition.

At the beginning of treatment with IVIG (baseline), all the patients showed a Urticaria Activity Score (UAS) of more than 35 points per week (sum of the daily scores), that is, more than 20 to 50 wheals daily and intense itching under treatment with the previously mentioned strategies.⁶ Table 1 describes the UAS.

Treatment Score

To assess the real effect of IVIG therapy by reviewing the individual treatment period, a specific score was chosen to judge the urticaria activity by observing the add-on therapy for the remaining urticaria symptoms (Table 2). We classified the severity of CSU in the patients at the beginning of the study and at each treatment cycle according to their need for add-on medication.

Dermatologic Examinations

Before treatment, all the patients were subjected to an extensive dermatologic examination to identify possible underlying causes of CSU.

Autoreactive Urticaria. In patients who develop positive ASST responses, that is, immediate hypersensitivity-like skin reactions to their own serum, CSU is widely regarded as representing a distinct subgroup (autoreactive CSU). The ASST was performed in all the patients before starting therapy, as described by Greaves⁷ and Staubach et al.⁸ Patients stopped using antihistamines and corticosteroids for 5 days before ASST, if possible. Autoantibodies such as thyroid autoantibodies also advert to an autoreactive or autoimmune origin.

Intolerance Urticaria. To exclude an underlying pseudoallergy, all the patients were subjected to a 21-day diet largely devoid of food additives, such as preservatives and colorants, natural pseudoallergens, and histamine, before treatment with IVIG.

Infectious Urticaria. Diagnostic procedures for identifying CSU due to infectious diseases included (1) blood testing for markers of infectious inflammation (hepatitis serology, C-reactive protein, erythrocyte sedimentation rate, fibrinogen, complement, and immune complexes), urease testing, and serum IgG antibodies against *Helicobacter pylori*; (2) clinical investigations to exclude infections of the intestinal or upper respiratory tract and nasopharynx, including maxillary sinusitis, streptococcal tonsillitis, and tooth infections; and (3)

Table 1. Assessment of Disease Activity in Urticaria^a

UAS	Wheals	Pruritus
0	None	None
1	Mild (<20 wheals/24 h)	Mild (present but not annoying or troublesome)
2	Moderate (20-50 wheals/24h)	Moderate (troublesome but does not interfere with normal daily activity or sleep)
3	Intense (>50 wheals/24 h or large confluent areas of wheals)	Intense (severe and sufficiently troublesome to interfere with normal daily activity or sleep)

Abbreviation: UAS, Urticaria Activity Score.

^a Sum of score: 0-6 daily.

Table 2. Treatment Score

Grade	Description
5	Recurrent CSU symptoms under immunosuppressive treatment (eg, corticosteroid, cyclosporine, or dapsone)
4	No symptoms under immunosuppressive treatment (eg, corticosteroid, cyclosporine, or dapsone)
3	Recurrent CSU symptoms under H ₁ antihistamines (up dosing) combined with leukotriene antagonists (montelukast) or H ₂ antihistamines
2	No symptoms with daily use of H ₁ antihistamines (up to 4-fold)
1	No symptoms with H ₁ antihistamines as needed
0	No symptoms, no therapy

Abbreviation: CSU, chronic spontaneous urticaria.

stool analysis for worm eggs, pathologic germs, parasites, and *Candida albicans*.

Urticaria Due to Other Reasons. To identify other possible causes of CSU, we performed prick testing, intracutaneous testing for molds and *Candida albicans*, and blood analyses (eosinophil cationic protein, total IgE, vitamin B₆, differential blood cell count, serum IgA and IgG, and rheumatoid factor, ultrasound, and x-ray of the thorax).

Patients

Patient SA. A 16-year-old boy with a CSU associated with angioedema for nearly 3 years (ASST positive; UAS range

before treatment, 35-42). Therapy with IVIG started after nearly 2 years of unsuccessful urticaria treatment strategies.

Patient BA. A 49-year-old man with CSU for more than 1 year (ASST positive; UAS range before treatment, 35-42). Therapy with IVIG was started after more than 1 year of therapy-resistant treatment strategies.

Patient SU. A 67-year-old woman with CSU and angioedema (ASST positive; UAS range before treatment, 35-42). Therapy with IVIG was started 2 years after unsatisfied treatment of CSU.

Patient DE. A 23-year-old man with CSU combined with angioedema for 11 years (ASST negative; UAS range before treatment, 35-42). The first cycle of IVIG was given after 11 years of unsatisfied treatment of CSU.

Patient LI. A 51-year-old woman with CSU for 2 years and severe angioedema (ASST positive UAS range before treatment, 35-42). Therapy with IVIG was started 10 years after the beginning of unsatisfied treatment of urticaria.

Patient LO. A 72-year-old woman with CSU that started 5 years earlier (ASST negative UAS range before treatment, 35-42). Therapy with IVIG was started 5 years after the beginning of ineffective treatment of urticaria.

RESULTS

The effects on these 6 patients were quite different concerning the amount of time and the treatment score (TS) needed until a stable response was reached (Fig 1). For a better understanding of the TS, we give the time points of infusion

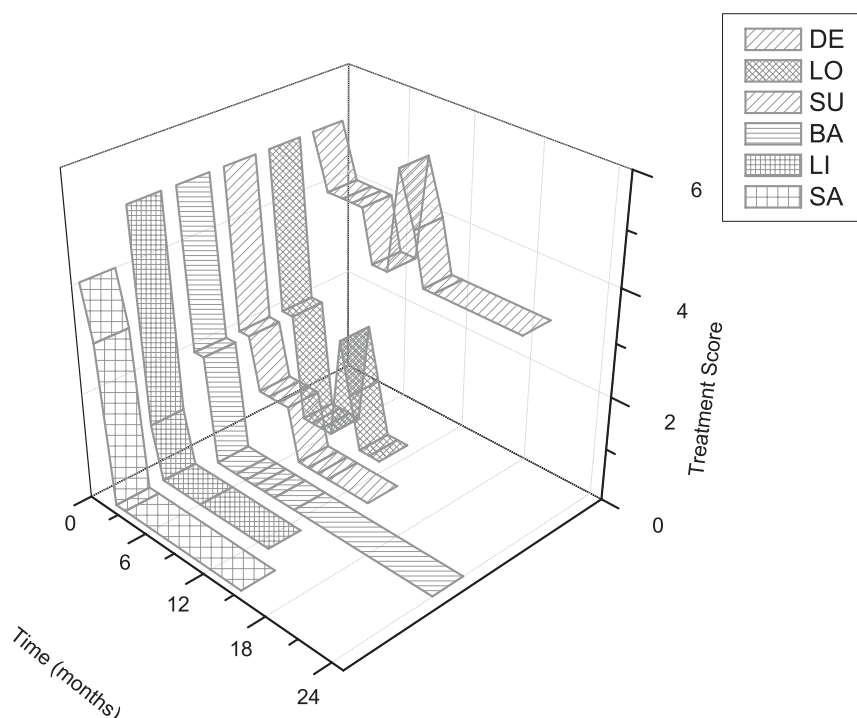


Figure 1. Relationship between treatment score and duration of treatment for each patient.

with IVIG in every patient in Table 3. The number of treatment cycles depended on the permission of the health insurance provider. Patients were followed up for a median of 16 months (range, 11-24 months).

Response to Treatment in Each Patient

Table 4 summarizes the important information for each patient. Patient SA, with CSU associated with episodic angioedema, showed complete remission of his urticaria (TS=0) after 3 cycles and stayed symptom free, with no need for further medication (at 15-month follow-up). Patient BA, with CSU, showed partial remission after 3 cycles (TS=1). After the fourth cycle, he was symptom free (TS=0). He received 6 additional treatment cycles and was symptom free after 24 months of observation. He does not take any additional or concomitant medications (TS=0). Patient SU, with CSU and recurrent angioedema, showed partial remission after 3 cycles (TS=1) and was symptom free after 11 cycles (TS=0), with follow-up of 14 months. Patient DE, with CSU and angioedema, only partially responded. After 4 cycles, he improved his TS from grade 5 to grade 3, and 7 additional cycles did not show a better effect (Fig 1). However, he significantly improved his school attendance compared with the time before treatment with IVIG. His follow-up was 20 months. Patient LI, with CSU and angioedema, was treated with 1 cycle of IVIG and had total remission; she does not need any antihistamines and has been symptom free for 13 months (TS=0). She also improved her sick hours at her place of work. Patient LO, with CSU and angioedema, responded totally after 4 cycles (TS=0); 2 months after the last treatment, she had a relapse up to TS=3, so IVIG treatment was reinitiated. After the fifth cycle, she improved again to TS=1.

Adverse Effects

Adverse effects observed in or reported by patients receiving IVIG included severe (patient SA) and moderate headache (patient DE), as well as impairment of preexisting hypertension (patients BA and LO). Although headache in patients SA and DE could be treated well by paracetamol administration, the preexisting hypertension of patient LO was more difficult to control, although the patient was taking antihypertensive drugs regularly. By extending the treatment period from 2 to 3 days, the adverse effect disappeared. Patient LI had recurrence of a preexisting but inactive hand eczema 1 month after treatment. Until today, it is not clear whether this is related to the therapy. It was controlled by psoralen-UV-A and local corticosteroid therapy and has disappeared.

Table 3. Time Points of Infusions in Each Patient

Patient	Time point of infusion in months from baseline
DE	0, 1.5, 3, 4, 5, 6, 7, 8, 10, 11, 12
BA	0, 1, 2, 3, 5, 6, 7, 8, 9, 11
LI	0
LO	0, 1, 2, 3, 7, 8, 9, 10, 11
SA	0, 1, 2, 3
SU	0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10

DISCUSSION

In general, patients with urticaria can be successfully treated using the current guidelines. In a few patients with therapy-resistant CSU or severe forms of physical urticaria, there is a need for IVIG, as mentioned in the newest guidelines for urticaria. For these reasons, and due to the high costs, only a few studies of successful treatment with IVIG in a small number of patients with CSU with different types of urticaria exist (delayed pressure urticaria,⁹ autoimmune urticaria,¹⁰ and solar urticaria¹¹⁻¹³). Although patients with delayed pressure urticaria had a favorable response, with long-lasting remission in 5 of 8 patients,⁹ another case report of 3 treated patients by Asero¹⁴ observed only a partial response to IVIG in the patient who had a positive histamine release assay. These case reports, under various conditions, lead to different conclusions concerning the underlying causes of urticaria as predictors of patient response to IVIG. In the past, we described a patient with severe CSU turning into urticaria vasculitis (hypocomplementemic). This patient was successfully treated with IVIG.¹⁵ In the present study, we observed 6 patients with CSU treated with IVIG. The study by O'Donnell et al³ and other newer studies with small numbers of patients, could also prove the effect of immunoglobulins, especially in autoimmune urticaria (ASST positive). The good response of patients with positive ASST reactions shown by O'Donnell is supported by the present findings: all 4 patients with positive ASST reactions before the start of IVIG therapy had a better response compared with the ASST-negative one with only slight improvement. However, many studies already established the effectiveness of IVIG for ASST-positive and ASST-negative patients.^{9,16}

We treated 6 patients who were different in their medical conditions concerning preexisting autoimmune disorders, thyroid autoantibodies, and other systemic diseases, such as diabetes mellitus. Five of them had a high benefit after only 1 to 3 cycles. The UAS and add-on treatment significantly decreased. The patients mostly had no more disease activity without any need for antihistamines or immunosuppressive therapies. Four of these patients showed remission during follow-up of more than 12 months. One patient, who also has a mental disorder and who affected his disease by taking diclofenac, responded only temporarily but could delimit his need for medication (as shown by his TS). Treatment with IVIG was effective regardless of the existence of other autoimmune disorders, which shows the broad application area of IVIG for different kinds of patients with CSU. The minor adverse effects, such as headache and increased blood pressure, are well known in this kind of treatment.

Regarding the impact of urticaria on quality of life, a substitution of daily immunosuppressive treatment by antihistamines and monthly IVIG infusions represents a remarkable improvement for a patient.⁶

O'Donnell et al³ also assumed that an additional course of IVIG may intensify the effect of immunoglobulin. These observations can be supported by the present investigations and are in

Table 4. Demographic and Clinical Characteristics of the 6 Study Patients

Patient	Urticaria and relevant medical history	Age, y/ Sex	Duration of CSU, y	ASST reaction before therapy	Infusions, No.	Outcome as TS	Follow-up, mo	Previous medications	Treatment-related AEs
SA	CSU, angioedema, autoimmune thyroiditis, IgA immunodeficiency	16/M	3	Positive	4	Remission (TS=0)	15	H ₁ and H ₂ antihistamines in 4-fold doses; leukotriene antagonists, high-dose corticosteroids	Severe headache, controlled well by medication
BA	CSU, Hashimoto thyroiditis, arterial hypertension	49/M	1	Positive	10	Remission (TS=0)	24	H ₁ and H ₂ antihistamines in 4-fold doses; leukotriene antagonists, high-dose corticosteroids	Impairment of preexisting hypertension, controlled well by medication
SU	CSU, angioedema, struma multinodosa type 2, diabetes mellitus	67/F	2	Positive	11	Remission (TS=0)	14	H ₁ antihistamines in 4-fold doses, leukotriene antagonists, cyclosporine, histaglobin	None
DE	CSU, keratokonius with cornea transplantation, thyroid antibodies, several hospitalizations	23/M	11	Negative	11	Improvement (TS=3)	20	H ₁ antihistamines in 4-fold doses, leukotriene antagonists, histaglobin, high-dose corticosteroids	Moderate headache
LI	CSU, angioedema, autoantibodies 1:320, intestinal <i>Candida</i> , hormone therapy	51/F	10	Positive	1	Remission (TS=0)	13	H ₁ and H ₂ antihistamines in 4-fold doses, leukotriene antagonists, dapson, high-dose corticosteroids, autologous hematotherapy, histaglobin	Reactivation of preexisting hand eczema (relation to treatment unknown)
LO	CSU, type 2 diabetes mellitus, hypertension, strumectomy, osteoporosis, relapsing angioedema, dyspnea	72/F	5	Negative	9	Remission (TS=0) after second start	11	H ₁ antihistamines in 8-fold doses, leukotriene antagonists, dapson, high-dose corticosteroids	Impairment of preexisting hypertension, hardly controlled by medication

Abbreviations: AE, adverse effect; ASST, autologous serum skin test; CSU, chronic spontaneous urticaria; TS, treatment score.

line with the experience with IVIG in autoimmune disorders such as dermatomyositis and bullous diseases, as noted by Rütter and Luger,¹⁶ where IVIG is used as a continuous treatment combined with other therapies. On the other hand, the present study reveals that a limited number of cycles with IVIG can induce prolonged remissions: 4 patients have been symptom free for a long time (10-24 months) without IVIG, an important fact concerning the costs compared with other new treatment options, such as omalizumab, also recommended by the new guidelines for CSU.² Omalizumab, an IgE antibody, showed very good effects on different forms of urticaria¹⁷⁻¹⁹ as well, although it needs to be given regularly every 2 or 4 weeks and continued for a very long time; furthermore, we know from clinical experience that discontinuing omalizumab use may lead to a fast relapse in severely affected patients.

The present findings show that treatment with immunoglobulins can induce significant improvement or cure in patients with severe therapy-resistant CSU. Besides the reduction in medication use, it can reduce the socioeconomic burden for patients.²

Although we know various immunomodulatory mechanisms of IVIG,⁵ the role of IVIG in autoimmune urticaria and other forms of urticaria is not clear and needs further investigations²; but, several studies could prove the benefit of this treatment option, particularly in patients with CSU. In summary, the present results and others strongly demand studies with larger numbers of patients. Owing to the high costs, those studies will not be performed specifically for patients with CSU in the near future. These results emphasize other results where IVIG is an effective treatment option for a CSU subgroup. These publications strengthen our request for health insurance providers to approve IVIG treatment in therapy-resistant cases of CSU.

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