LOW-DOSE INTRAVENOUS GAMMAGLOBULIN IN THE TREATMENT OF SEVERE AUTOIMMUNE URTICARIA

C. Pereira (1), B. Tavares (1), I. Carrapatoso (1), G. Loureiro (1), E. Faria (1), D. Machado (1), C. Chieira (1)

SUMMARY

**Background:** An autoimmune pathogenic mechanism is implicated in about one-third of patients with chronic urticaria (CU), involving circulating functional autoantibodies to either the high affinity IgE receptor (IgG1/IgG3 anti-FcεRI) or to IgE, with histamine releasing activity.

New therapeutic approaches had been developed for patients with severe or unresponsive to treatment symptoms, including the use of Intravenous immunoglobulins (IVIG) as immunomodulators.

**Aim:** To assess the efficacy of IVIG treatment in patients with evidence of autoimmune CU.

**Methods:** A group of 29 patients (F=20, M=9) with the diagnosis of autoimmune CU were selected from the outpatient department. All the patients showed daily symptoms of urticaria and/or angioedema, with unsatisfactory response to conventional therapy and a positive intradermal autologous serum test (AST). They were submitted to low dose of IVIG treatment each 4 weeks (0.15g/kg), for a minimum of 6 months and a maximum of 91 months. They were evaluated for clinical scores, need of oral medication and AST results, before and after treatment.

**Results:** A clinical improvement was observed in 26 patients, with reduction of urticaria or angioedema complaints (p=0.001) and decreasing need for oral antihistamine medication (p=0.002). 3 patients drop-out the treatment, one depending on severe adverse event and the other 2 with no response after the 6th treatment. 19/26 patients achieved complete remission of symptoms. A reduction of histamine-releasing activity was found in the majority of the patients, documented by the decrease of reactivity in AST at the end of the treatment (p=0.002). 20 patients remained without symptoms during 12 months after the active treatment, and the other 6 only reported non-severe complaints.

**Conclusion:** IVIG is an effective therapeutic option in patients suffering from severe CU refractory to conventional treatment, in which autoimmune mechanism is involved. The efficacy persists for at least 12 months after treatment. However, the number of infusions needed to achieve clinical control, showed great range between patients.

**Key-words:** Chronic urticaria - Autoimmune - Immunoglobulin - IVIG - Urticaria treatment.

INTRODUCTION

Urticaria is a multifactor disorder characterized by the presence of widespread recurrent hives, cutaneous itching, with individual lesions lasting less than 24h (1, 2), without residual or infiltrated skin during relapses. These clinical criteria are needed for diagnosis. Acute episodes are common among general population, and generally they are self-limited or promptly disappear after adequate treatment. The recent guidelines concerning urticaria are highly useful in order to schedule and organize a set of procedures, namely clinical, diagnostic and therapeutic (2). Chronic urticaria is a heterogeneous syndrome that may be elicited by a great diversity of factors and clinically presents high variability (1-2). It is defined as the daily or almost daily occurrence of wheals for 76 weeks. Physical urticaria and urticarial vasculitis are excluded from this definition. Although the mechanism is unclear, some patients experiment exacerbation by components of foods, such as salicylates, benzoes or nitrates (2).

There are three disease subsets in CU: first, autoantibody mediated 29% (anti-FceRI and anti-IgE); second, direct mast cell histamine releasing activity 31% and; third, autologous serum test negative patients 40% (3).

The suggestion of autoimmune pathogenesis in CU was made by the demonstration of IgG anti-FcεRI and anti-IgE autoantibodies capable of activating mast cell and basophil degranulation in a subset of patients (2-6). These autoantibodies are related to disease exacerbation (7). The presence of this autoimmune disorder in chronic urticaria patients is no consensual in the literature; however Grassani et al. suggested an incidence of about 30% (7-9).

These autoantibodies have not been identified in patients with psoriasis, dermographism or cholinergic urticaria, or in healthy control subjects (5). Anti-FcεRI autoantibodies have been found in other autoimmune diseases, such as SLE or dermatomyosi-
tis, but they are not able to release histamine from basophils or mast cells. Another difference is the IgG isotype: IgG2 and 4 in systemic autoimmune disease and IgG1 and 3 on patients with autoimmune urticaria (9).

A correlation between the presence of anti-FceRI and anti-IgE autoantibodies and positive intradermal autologous serum test (AST) was documented (6, 10). As a result, in clinical practice, a positive test is assumed to be suggestive of the autoimmune pathogenesis of the urticaria (10). Basophils are frequently used as an in vitro surrogate for mast cells, and secretion of histamine as a result of incubation with patient sera or purified IgG was readily demonstrated (11). The incidence of a positive assay result was generally higher than that observed with the AST (10-14). Thus, functional autoantibodies appear to be specific to a set of patients suffering chronic urticaria (14).

At present there is little experience on the managing of severe patients with autoimmune urticaria. The clinical pattern of high severity and unresponsiveness to classical treatment is an ethical obstacle to perform controlled blind studies with other therapeutic options in these patients.

There are only a few studies with highly aggressive treatments in patients with autoimmune subsets of chronic urticaria (15). Plasmapheresis by removing autoantibodies had been showed only temporary benefit; cyclosporine-A had been proven to be helpful but with rebound effect after treatment stopped (16-20). Intravenous high dose of immunoglobulin (IVIG) infusion was tried in patients with autoimmune CU, but without longer follow up after the interruption of treatment19.

The aim of the present open clinical study was to assess the efficacy of low dose intravenous gamma globulin treatment in patients with severe disease or unresponsiveness to treatment and evidence of autoimmune CU.

**MATERIAL AND METHODS**

**Patients**

This study was carried out between 1997 and 2006 in the Immunology Department of Coimbra University Hospital. All the treatments had the official agreement of the Executive Office of the institution. A written informed consent form was obtained from all the patients before entering the study.

Twenty nine patients suffering from severe chronic urticaria non-respondent to conventional therapy were select. Angioedema was associated in 11 patients, 5 of them requiring systemic steroids for partial clinical control. All the patients were submitted to extensive diagnostic procedures including: immunological parameters, allergic study, virus and bacterial serology, auto-antibodies determination, thyroid evaluation and skin biopsy. All of them presented intradermal positive skin test with autologous serum. All the patients were additionally submitted to different anti-histaminic therapy schedules (at least 2 distinct non sedating medications a day) and without complete remission of symptoms. They maintained daily appearance of hives, frequent exacerbations and frequent need of systemic corticosteroid bursts. Besides the clinical severity they are patients with markedly interference on live quality and limiting social activities.

**Methods**

All the patients were submitted to a clinical and laboratorial evaluation previously to the starting of treatment with IVIG. The clinical evaluation was repeated each 4 weeks. An additional period of one year of observation was performed after the end of IVIG treatment.

- **Clinical evaluation.** A careful clinical history concerning infection, occupational exposure, medications or foods, and a full physical examination were performed in all patients. A restrictive regimen of foods rich in biological amines and preservatives did not showed clinical benefit. All the patients presented daily symptoms of urticaria despite being compliant with the therapeutic plan. The symptoms and consumption of medication were scored according to grades as in table 1 and 2 respectively.

| I. Absence of symptoms |
| II. 1-2 episodes of urticaria and/or angioedema per month |
| III. 1-2 episodes of urticaria and/or angioedema per week |
| IV. Daily symptoms of urticaria and/or angioedema. |

**Table 1:** Score of symptoms.

| 0. No medication |
| 1. 4 anti-histamine tablets per month |
| 2. More than 4 anti-histamine tablets per month |
| 3. Daily use of anti-histamine |
| 4. Daily use of systemic steroids and anti-histamine |

**Table 2:** Score of medication needs.

**Laboratorial evaluation.** All the patients were previous submitted to the following study: differential blood count, erythrocyte sedimentation rate, seric immunoglobulin and complement determinations, serological tests to bacterial and virus, autoantibodies, thyroid evaluation, stool examination for worm eggs/parasites and sinus scan. Besides these procedures all of them had a previous normal skin histological examination. The allergy study was also negati-
ve, namely skin prick tests to aeroallergens and foods. All the patients had normal renal, hepatic and cardiovascular function routine tests, as well as normal serum IgA levels.

- **Intradermal autologous skin test (AST).** The skin test was performed before starting treatment, as described by A Fusari et al. (10), with the intradermal injection of 0.03cc of autologous serum. The results were measured 20 minutes later. The test was regarded as positive for a wheal diameter of at least the same diameter (mm) induced by histamine. The test was repeated at the final of the treatment.

- **Immunoglobulin treatment.** The patients were treated on an in-patient basis with intravenous immunoglobulin (Sandoglobulina, ZLB Bioplasm AG, Bern, Swiss.), 0.15g/kg each 4 weeks. Each patient started treatment with a personalized therapeutic plan. In case of acute exacerbation of urticaria they were allowed to take cetirizine 10 mg per os.

The IVIG treatment was performed for a minimum period of 6 months, extending longer depending on the clinical response of each patient. For this reason we considered different groups concerning the duration of active IVIG treatment: Group A: ≤ 6 months of treatment (n=9); Group B: 7 to 12 months (n=12); Group C: ≥ 13 months of treatment (n=8). The treatment was interrupted in case of absence of clinical improvement after at least 3 additional infusions.

- **Statistical analysis.** Statistical analysis was performed by using SPSS software, 14.0 version. Frequency distribution analysis, means and standard deviation (SD) were obtained. The urticaria activity scores, the consumption of medication and the AST values after treatment were compared with the pre-treatment values for the entire sample (Wilcoxon matched pairs). The same procedure was applied considering the group of patients which performed ≤ 6 months of treatment (Group A), 7 to 12 months (Group B) and ≥ 13 months (Group C) of IVIG treatment. A p value < 0.05 was regarded as statistically significant.

**Results**

From the 29 patients included on the study, 20 were female, with an average age of 45.59±10.868 years (22 to 61 years). The mean disease duration was 9 years (1-32 yrs). The dose of IVIG administered per infusion ranged between 5 to 12 g.

A serious adverse event was observed in one patient after the second IVIG administration. An acute episode of urticaria, vascular hypotension, tachycardia, chest tightness and sudoresis 15 minutes after the perfusion was observed. The patient promptly recovered after medication, and drop-out of the study.

In other two patients the treatment was interrupted after the 6th IVIG administration because of the absence of clinical improvement and drug consumption. Except for one patient that presented minor paresthesias and discrete increase in symptom scores subsequent to the first two treatment sessions no other side effects were observed during the study.

The other 26 patients showed evidence of clinical benefit with IVIG treatment. The length of active therapy ranged from 6 to 51 months. The beginning of consistent clinical improvement after starting IVIG treatment was also variable (from 1 to 13 months; mean 4.5 months).

Patient score of symptoms before and after treatment is shown in figure 1. There was a significant improvement considering the whole sample (p<0.0001), as well as in the evaluation considering the different groups (Group A p=0.02; Group B, p=0.002; Group C p=0.014).

The score of medication needs before and after IVIG treatment is shown in figure 2. There was a significant reduction of medication needs after the treatment (p=0.002). The differences were also significant in group A (p=0.046). Despite an improvement in Groups B and C, the differences had no statistical significance (p=0.08 and p=0.10 respectively).

From the 26 patients that showed clinical improvement 3 of them required systemic steroids in the beginning of the active treatment. Only one patient persisted dependent on corticosteroids, but with a reduced dose (16 to 8 mg of methylprednisolone).

![Figure 1: Score of symptoms before and after IVIG treatment.](image1)

![Figure 2: Score of medication needs before and after IVIG treatment.](image2)
Another patient maintained daily systemic antihista-
mine treatment to prevent the occurrence of hives
and the other one completely reduced the need of
medication.
Two patients that failed to prove clinical benefit after
5 IVIG administrations, drop-out the study. They were
also steroid-dependent and maintained the same
dose of systemic corticosteroid during the 20 weeks
of treatment. The third patient that drop-out the study
because of a severe adverse event, was only on two
different anti-histamines per day.
The analysis of AST results before and after IVIG
treatment showed a significant reduction of the wheal
diameter after treatment (p=0.002). Eighteen patients
out of the 26 that showed clinical efficacy with IVIG
treatment showed an AST wheal reduction, in 3
patients the AST remained unchanged and in 5
patients it raised (Figure 3).
Concerning cutaneous histamine reactivity, 11
patients showed a slight reduction in the histamine
wheal diameter, and the other 11 patients an increase
(p=0.90) (Figure 4).

![Figure 3: Autologous serum intradermal test results (wheal
diameter in mm) before and after IVIG treatment.](image)

![Figure 4: Histamine skin reactivity (wheal diameter in mm)
results before and after IVIG treatment.](image)

There were no changes on the skin reactivity to histami-
ne and AST in the 2 patients that did not showed clinical
benefits with the IVIG administration or in the patient
that drop-out the study after serious adverse event.
There was no clinical rebound during the 12 months
after stopping the IVIG treatment in the 26 patients
that had shown clinical improvement. 20 patients
remained without need of medication and the other
6 only one to two times a month. We stress the case
of one patient that one year after stopping IVIG treatment was able to finally stop systemic corticosteroid.

**DISCUSSION**

Clinical and experimental evidence suggests that a
wide spectrum of immune-mediated diseases benefit
of the use of IVIG (22). Most preparations contain
traces of IgA, and carry the risk of sensitization to IgA
in long-term treatment of IgA-deficient individuals. The
preparations contain intact Fc moieties which allow
IVIG to interact with and signal through Fc receptors on
Fc receptor-expressing cells (phagocytes and B cells)
and with a number of Fc-binding plasma proteins
(complement system) (23). The mode of action of IVIG
is complex and not completely known. However it has
been described a modulation of expression and func-
tion of Fc receptors, interference with complement acti-
vation and cytokine network, provision of anti-idiotypic
antibodies, inhibition of maturation and function of
dendritic cells, modulation of T and B cell activation,
namely on differentiation and effector functions (24).
The ability of IVIG to interact through V regions with
complementary V regions of antibodies and antigen
receptors as well as with relevant soluble and surface
molecules provides the basis for inducing the selection
of immune repertoires (23).

As far as we know, there are only 2 papers in the lit-
erature regarding the use of high dose of IVIG
(0.4g/kg/day for 5 days) in autoimmune CU patients
with severe symptoms and unresponsiveness to
conventional therapy (10 and 3 patients respectively),
showing divergent results (21, 25).

Another study, reports IVIG higher dose administra-
tion (2g/kg given over 2-3 days) in 8 delayed pressure
urticaria patients, 4 of them AST positive (26).
Other 2 case reports showed efficacy of IVIG in CU
(0.2 g/kg for 1 day repeated every 4 weeks) and in
solar urticaria (2.5 g/kg given over 3 days) (27, 28).
The present study included the most severe patients of
our outpatient department suffering from this chronic
disease. All of them had been submitted to serial labora-
torial determinations since the first medical observation.
Most antihistamines had been tried in monotherapy with
increased doses or in association. Dietary restrictions on
foods rich on biological amines, salicylates and preserve-
tives were also recommended. However they persisted
with daily symptoms and frequent exacerbations. Some of
them required systemic steroids for partial control.
The AST was strongly positive in all patients, with a
wheal diameter always higher than that induced by
histamine.

The in vitro histamine releasing test from basophils
was not performed, because of its low sensitivity. As
a positive AST in clinical practice is assumed to be suggestive of the autoimmune pathogenesis (9, 10, 29) we decided to evaluate our patients with this test. Comparing with the results of O'Donnell et al. (21), the majority of our patients maintained clinical remission after stopping IVIG (one year follow-up). However the dose in our study (0.15g/kg) was lower and repeated each 4 weeks.

We believe that a consistent immunomodulatory effect is reached by subsequent repeated low dose IVIG administration opposed to a high blocking effect of IVIG high dose that would result in an increased IgG catabolism (30), so the need of readministration. In those patients, the clinical response was determinant for the maintenance of IVIG treatment. The consistent clinical improvement only occurred after several administrations (mean 4.5 months) and it was gradual and progressive for each patient. There are several spectrums of response, dependent of the autoimmune CU heterogeneity. The clinical scores and need of medication used for evaluation of efficacy of treatment are considered to be better indicators of disease activity than AST, which was already assumed not being a good predictor of IVIG response (26). Twenty six patients showed clinical benefit with IVIG treatment. Only two patients did not improve. Despite the severe side effects that occurred in one patient, IVIG treatment was well tolerated and is considered to be safe (31).

IVIG low dose repeated each 4 weeks is effective for the treatment of severe or unresponsive autoimmune CU patients that failed to control disease by conventional therapy. The evaluation one year later showed persistent clinical benefit, with absence of symptoms in 20 patients and reduction of symptoms in the other 6 patients. The kind of response to IVIG treatment is not predictable. The results of these studies are difficult to understand since some patients maintain additional therapy and the disease has different grades of severity. There are limitations concerning ethical aspects that obstruct the performance of placebo control double-blind studies to evaluate the efficacy of this treatment. The cost and reduced availability of the product are restrictive for use in daily practice and also impeditive of large sample trials in order to license IVIG for the treatment of severe autoimmune CU.

References