

## Intravenous immunoglobulin in autoimmune chronic urticaria

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### Summary

Histamine releasing autoantibodies play a central role in the pathogenesis of chronic urticaria (CU) in approximately 30% of affected patients. We investigated the therapeutic effect of high-dose intravenous immunoglobulin (IVIG) on disease activity in patients with severe CU of autoimmune aetiology. Autoimmune urticaria was diagnosed by the development of a weal-and-flare reaction to the intradermal injection of autologous serum and by serum-induced histamine release from the basophil leucocytes of healthy donors *in vitro*. Ten patients with severe, autoimmune CU, poorly responsive to conventional treatment, were treated with IVIG 0.4 g/kg per day for 5 days. The outcome on cutaneous wealing and itch was monitored using urticaria activity scores, visual analogue scales and autologous intradermal serum tests. Clinical benefit was noted in nine of 10 patients; three patients continue in prolonged complete remissions (3 years follow-up), two had temporary complete remissions, and symptoms in four patients improved subsequent to treatment. There was significant improvement in the urticaria activity scores and visual analogue scores at 2 ( $P < 0.01$ ) and 6 weeks ( $P < 0.01$ ) post-IVIG compared with the baseline values (Wilcoxon matched pairs). The diminution in urticarial activity in the majority of patients corresponded with a reduced weal-and-flare response to the intradermal injection of autologous post-treatment serum compared with the pretreatment serum. Minor side-effects were common, but there were no serious or long-term adverse effects. IVIG represents a novel therapeutic option in selected patients with recalcitrant CU associated with histamine releasing autoantibodies.

We define chronic urticaria (CU) as a 6 week or longer history of daily or almost daily, widespread, itchy cutaneous swellings (weals) with individual lesions lasting less than 24 h.<sup>1</sup> The disease follows a protracted course in a significant percentage of patients attending hospital clinics.<sup>2</sup> The majority of patients with CU have been labelled as 'idiopathic',<sup>2</sup> but more recently the intradermal injection of autologous serum suggested the involvement of one or more serological mediators.<sup>3,4</sup> Evidence of mast cell degranulation in the serum-induced weals was found in light and electron microscope studies.<sup>5</sup> We demonstrated in a recent study that 98 of 163 (60%) patients with CU had positive autologous intradermal serum tests during the active phase of their disease.<sup>6</sup> The sera from 47 of the 98 (29% of total CU patients) skin-test-positive patients also released histamine *in vitro* from the basophil leucocytes of healthy donors. This histamine-releasing activity has

been identified as due to IgG autoantibodies directed either against IgE<sup>7</sup> in 5.5% of CU patients<sup>6</sup> or against an epitope or epitopes in the alpha chain of the high-affinity IgE receptor, FcεR1, in 23% of patients.<sup>6</sup> These autoantibodies mimic the cross-linking of specific IgE on FcεR1 by antigen thus leading to the release of histamine from basophil leucocytes and mast cells.<sup>6–8</sup> The above findings have recently received independent confirmation.<sup>9,10</sup> More recently, sera from the remaining autologous intradermal serum test positive patients that fail to release histamine from basophil leucocytes, have been shown to contain a mast-cell-specific histamine-releasing factor.<sup>11</sup> Although this factor remains to be fully characterized, it can be differentiated from anti-FcεR1α or anti-IgE antibodies.<sup>11</sup>

The concept of an autoimmune aetiology<sup>12</sup> for some cases of CU is supported by its association with autoimmune thyroid disease,<sup>13</sup> and with HLA DR4.<sup>14</sup> That functional anti-FcεR1 autoantibodies underlie the pathogenesis of this subset of CU patients is also supported by the direct relationship between serum

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histamine-releasing activity on donor basophil leucocytes and disease activity in patients treated by plasmapheresis.<sup>15</sup>

Intravenous immunoglobulin (IVIG), a polyvalent antibody product derived from the pooled plasma of healthy donors, has been used successfully in the management of autoimmune disorders including idiopathic thrombocytopenic purpura<sup>16</sup> and antineutrophil cytoplasm antibody (ANCA) positive vasculitis.<sup>17</sup> Its mode of action is incompletely understood but may involve blockade of receptors for the Fc portion of IgG molecules on reticuloendothelial cells, inhibiting the destruction of autoantibody coated platelets.<sup>16</sup> IVIG may also modulate the anti-idiotypic network and may have a direct inhibitory effect on B-cell function and/or T-cell function.<sup>18</sup> We have investigated the response of 10 patients with severe, unrelenting CU who had evidence of histamine releasing autoantibodies, to a 5-day course of IVIG.

## Patients and methods

Patients were recruited from the urticaria clinics at St John's Institute of Dermatology. All had severe CU which was causing significant disruption of personal, occupational or social life and was poorly responsive to conventional treatment with antihistamines. All patients had evidence of serum histamine-releasing activity as shown by a positive autologous intradermal serum test.<sup>7,8</sup> In addition, sera from all patients evoked positive (>5%)<sup>6</sup> histamine release *in vitro* from the basophil leucocytes of healthy donors, as previously described.<sup>6-8</sup> The two donors were selected on the basis of different degrees of endogenous IgE sensitization of their basophil leucocytes.<sup>6</sup> The basophil leucocytes of donor 1 were poorly sensitized to IgE, giving  $2.8\% \pm 1.7$  ( $n=11$ ) histamine release with 1:1000 dilution of polyclonal goat antihuman IgE, while the basophil leucocytes of donor 2 released  $47.1\% \pm 7.6$  ( $n=8$ ) histamine in response to anti-IgE. The mean ( $\pm$  standard deviation) serum-induced histamine release from the basophil leucocytes of donor 1 was  $32.4\% \pm 14.8$  and from those of donor 2 was  $28.7\% \pm 16.1$ . Sera from nine patients released histamine from the basophil leucocytes of both donors indicative of anti-Fc $\epsilon$ R1 autoantibodies.<sup>6,8</sup> Serum from one patient (no. 3) released histamine (19%) from donor 2 (IgE sensitized), but did not induce significant histamine release from the basophil leucocytes of donor 1 (3%, IgE non-sensitized). This patient was judged to have anti-IgE autoantibodies.<sup>6,8</sup> No

patient had been taking the long-acting antihistamine, astemizole. No patient was taking immunosuppressive treatment at the time of the study. All patients had normal renal, hepatic and cardiovascular function on routine tests, and all had normal serum IgA levels.<sup>19</sup>

Patients were treated on an in-patient basis with IVIG (Sandoglobulin®, Novartis, Frimley, U.K.) 0.4 g/kg per day for 5 days administered intravenously as a 3% solution in normal saline on the first day, followed by a 6% solution on the succeeding 4 days. Symptomatic treatment for headache was with paracetamol. During the study all patients took the same antihistamine, cetirizine 10 mg twice daily. Cetirizine was discontinued for 48 h prior to all skin tests.

Patient assessments were carried out at baseline (week prior to treatment), at day 1 post-treatment, at weeks 2 and 6 post-treatment, and six weekly until relapse or week 24, whichever occurred first.

### *The urticaria activity score*

The urticaria activity score was compiled from a self-assessment score sheet<sup>20</sup> adapted for the current study, which each patient recorded daily. The score sheet indicated the number of small (diameter <3 cm) and large (diameter >3 cm) weals and the severity of the itch. The number of weals was scored from 0 to 3: 0, <10 small weals; 1, 10–50 small weals or <10 large weals; 2, >50 small weals or 10–50 large weals; 3, almost covered.

The severity of the itch was also graded from 0 to 3: 0 = none; 1 = mild; 2 = moderate; 3 = severe. Therefore, the urticaria activity score ranged from 0 to 42 per week.

### *Visual analogue scale*

A visual analogue scale referring to overall urticaria severity during the preceding 2 weeks was completed by the patient at each follow-up appointment. The scale ranged from 0 to 10, 0 indicating no disease and 10 indicating very severe urticaria.

### *The autologous intradermal serum test*

Autologous intradermal serum tests were carried out as previously described<sup>7,8</sup> with some modification. Antihistamines were discontinued at least 48 h prior to skin testing. Briefly, venous blood was left to clot in sterile glass tubes for 20 min at room temperature. The blood was centrifuged at 1050 *g* for 15 min. Fifty  $\mu$ L aliquots

of undiluted autologous serum, saline (negative control) and histamine (10 mg/mL in saline, positive control) were injected at least 5 cm apart into the dermis of the volar aspect of the forearm. Two orthogonal diameters of the resulting papules or weals were measured immediately and at 30 min post-injection. A positive skin test response was arbitrarily defined as the development of a serum-induced weal-and-flare with the mean weal diameter at least 2 mm greater than the mean diameter of the papule induced by saline. Autologous intradermal serum tests were repeated comparing the skin reactions with the pretreatment sera with those using sera obtained after IVIG. All autologous intradermal serum tests were carried out by the same investigator (BO'D).

#### Statistical analysis

The urticaria activity scores and visual analogue scores post-treatment were compared with the pretreatment values (Wilcoxon matched pairs test).  $P \leq 0.05$  was considered statistically significant.

## Results

Ten patients (eight female), mean age 42.6 years, (range 24–75 years), mean disease duration 33.8 months (range 5–96 months) were treated. The majority had previous trials of various treatments, most commonly antihistamines, corticosteroids and cyclosporin (Table 1). Laboratory investigations prior to IVIG showed some minor abnormalities: elevated erythrocyte sedimentation rate (26, 21 mm in the first hour—two patients) and microcytic anaemia due to  $\alpha$  thalassaemia trait (one patient). IgE was raised in one

patient (215; normal range  $< 81$  kU/L) and two patients had an elevated IgM. Serum complement (C3, C4) was normal in all patients and one patient had a positive antinuclear antibody in low titre (1:10).

#### Urticaria activity scores

The results are shown in Figure 1. Patients 1 and 2 showed a striking clinical response with a complete remission of CU which was sustained at the final study visit at 24 weeks post-treatment and remains sustained 3 years post-treatment. Three patients (3–5) had a complete remission but relapsed after intervals of 6, 8 and 21 weeks, respectively. In patients 6–9 the urticaria improved and in patient 10 there was transient improvement only. There was significant improvement in the urticaria activity scores at 2 ( $P < 0.01$ ) and 6 weeks ( $P < 0.01$ ) post-IVIG compared with the baseline values (Wilcoxon matched pairs). The mean urticaria activity score improved from a baseline value of 24.6–12.6 and 7.8 at 2 and 6 weeks post-treatment, respectively (Table 2).

Two relapsed patients were offered a second course of treatment. Patient 4 who had an initial complete remission of 9 weeks received IVIG after an interval of 4 months. Repeat treatment afforded her a further temporary complete remission (6 weeks). Patient 5 was retreated within 4 weeks of relapse and had a prolonged complete remission following a second 5 day course of IVIG (Fig. 2), which is sustained 3 years later.

#### Visual analogue scores

The visual analogue scores (VAS) reflected the clinical improvement experienced by the majority of

**Table 1.** Gender, age, duration of continuous urticaria and previous treatments of patients with chronic urticaria treated with intravenous immunoglobulin (IVIG)

| Patient | Sex, age (y) | Continuous urticaria (months) | Previous treatments                                                                 |
|---------|--------------|-------------------------------|-------------------------------------------------------------------------------------|
| 1       | F, 39        | 96                            | antihistamines, cyclosporin                                                         |
| 2       | F, 34        | 28                            | antihistamines, prednisolone, danazol                                               |
| 3       | M, 32        | 24                            | antihistamines, prednisolone, dapsone, cyclosporin                                  |
| 4       | F, 35        | 60                            | antihistamines, sodium cromoglycate, prednisolone, stanozolol, dapsone, cyclosporin |
| 5       | F, 49        | 8                             | antihistamines, sodium cromoglycate, prednisolone, cyclosporin                      |
| 6       | M, 56        | 16                            | antihistamines                                                                      |
| 7       | F, 75        | 5                             | antihistamines                                                                      |
| 8       | F, 24        | 60                            | antihistamines                                                                      |
| 9       | F, 56        | 36                            | antihistamines, prednisolone                                                        |
| 10      | F, 26        | 5                             | antihistamines, plasmapheresis                                                      |

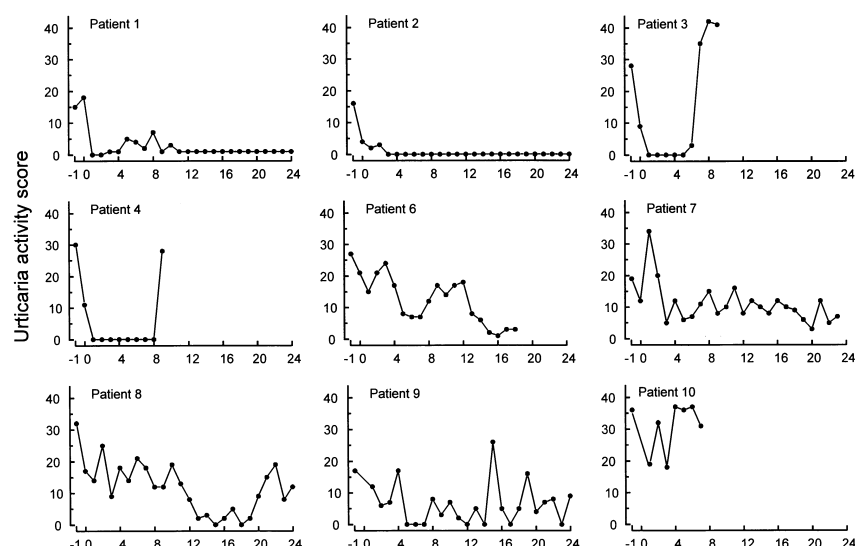


Figure 1. Urticaria activity scores following a single course of intravenous immunoglobulin (IVIG).

patients. The mean visual analogue score improved from 5.6 prior to treatment to 2.4 and 1.8 at 2 and 6 weeks post-IVIG, respectively (Table 3). The improvement in the VAS at 2 ( $P < 0.01$ ) and 6 weeks ( $P < 0.01$ ) was significant (Wilcoxon matched pairs).

#### The autologous intradermal serum test

Autologous intradermal serum tests at 1 and 14 days post-treatment showed a reduced weal-and-flare response to post-treatment sera compared with pre-treatment sera when the paired sera were tested simultaneously in seven of 10 patients (Fig. 3). The skin test

responses to pre- and post-treatment serum were similar in one patient (no. 7) and in patients 3 and 10 the skin test response to the post-treatment serum was greater. In patients with a complete permanent remission the skin test response was negative 24 weeks post-IVIG.

#### Adverse events

All patients suffered headache which was severe in six patients, occasionally associated with photophobia, and migraine-like in one man. Nausea (five patients), a low-grade pyrexia (four patients), phlebitis at the intravenous infusion site (three patients), and flu-like

Table 2. Urticaria activity scores before and after treatment with intravenous immunoglobulin (IVIG)

| Patient    | Baseline | Urticaria activity score: |                   |                       |
|------------|----------|---------------------------|-------------------|-----------------------|
|            |          | 2 weeks post-IVIG         | 6 weeks post-IVIG | 24 weeks post-IVIG    |
| 1          | 16       | 3                         | 0                 | 0                     |
| 2          | 15       | 0                         | 3                 | 0                     |
| 3          | 28       | 0                         | 3                 | relapse (6 weeks)     |
| 4          | 35       | 3                         | 0                 | relapse (8 weeks)     |
| 5          | 21       | 16                        | 0                 | relapse (21 weeks)    |
| 6          | 27       | 21                        | 7                 | 3                     |
| 7          | 19       | 20                        | 7                 | 7                     |
| 8          | 32       | 25                        | 21                | 12                    |
| 9          | 17       | 6                         | 0                 | 9                     |
| 10         | 36       | 32                        | 37                | transient improvement |
| Mean score | 24.6     | 12.6                      | 7.8               |                       |

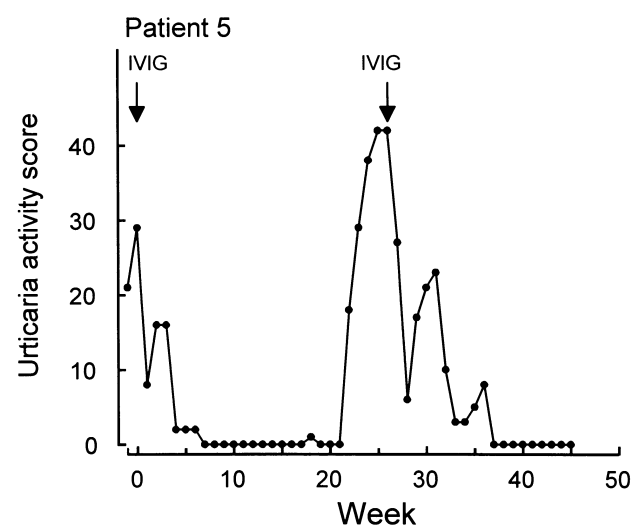


Figure 2. Urticaria activity scores for patient 5 following two courses of intravenous immunoglobulin (IVIG).

**Table 3.** Visual analogue scores (VAS) before and after treatment with intravenous immunoglobulin (IVIG)

| Patient  | Baseline | Visual analogue score (VAS) |                   |                       |
|----------|----------|-----------------------------|-------------------|-----------------------|
|          |          | 2 weeks post-IVIG           | 6 weeks post-IVIG | 24 weeks post-IVIG    |
| 1        | 2.8      | 1.4                         | 0.2               | 0                     |
| 2        | 2.8      | 0.1                         | 0                 | 0                     |
| 3        | 6.6      | 0.4                         | 1.0               | relapse (6 weeks)     |
| 4        | 4.4      | 0.3                         | 0                 | relapse (8 weeks)     |
| 5        | 4.0      | 2.7                         | 0.2               | relapse (21 weeks)    |
| 6        | 6.3      | 3.0                         | 2.2               | 1.4                   |
| 7        | 8.5      | 1.6                         | 1.5               | 4.0                   |
| 8        | 5.6      | 4.5                         | 3.7               | 1.5                   |
| 9        | 7.7      | 5.0                         | 0.7               | 4.8                   |
| 10       | 7.0      | 5.3                         | 8.7               | transient improvement |
| Mean VAS | 5.6      | 2.4                         | 1.8               |                       |

symptoms (two patients) also occurred. Two patients developed vesicular hand eczema. Renal and liver function remained normal in all patients and there were no long-term adverse sequelae.

## Discussion

The subset of CU patients whose disease is caused by histamine releasing autoantibodies may benefit from manipulation of the immune system. Plasmapheresis offers temporary response in some patients but is unlikely to prevent the re-accumulation of the autoantibodies.<sup>15</sup> IVIG is a less expensive option and our study indicates that it offers the possibility of a prolonged remission. A single course of IVIG afforded two patients a dramatic clinical response with complete remission of their urticaria. A third patient had a complete remission following a second course of IVIG. The disease remissions are prolonged: the three patients remain symptom-free 3 years post-treatment. In the remainder IVIG caused a temporary complete remission (two patients), improvement (four patients) or transient improvement (one patient). The variation in responses following IVIG may reflect batch variation in the product, individual disease factors, or the non-specific aggravation of CU by stress, hormonal factors, diet and drugs. The optimum dose of IVIG has not been determined for some of the established indications for IVIG.<sup>21</sup> That CU patients showing a temporary or incomplete response may benefit from a further course or courses of IVIG is suggested by the complete remis-



**Figure 3.** Autologous intradermal serum test at 2 weeks post-treatment with intravenous immunoglobulin (IVIG), showing the reduction in the wheal-and-flare response to the intradermal injection of autologous post-treatment serum compared with the pretreatment serum.

sion (to date) of patient 5 following a second course of IVIG. *In vitro* sequential analysis of her sera showed that the total serum histamine releasing activity from donor basophil leucocytes and that due to IgG anti-Fc $\epsilon$ R1 $\alpha$  correlated with clinical improvement.<sup>22</sup> Diminution in serum histamine releasing activity is suggested in a further six patients by a reduction in the wheal-and-flare response following the intradermal injection of autologous post-treatment serum compared with the pretreatment serum at 1 day and 2 weeks following a single course of IVIG (Fig. 3).

IVIG differs significantly from other immunosuppressive agents and represents a novel therapy for the dysfunctional immune system in a number of autoimmune diseases. IVIG is known to induce a fall in autoantibody titres, for example anti-DNA,<sup>23,24</sup> anti-thyroglobulin,<sup>24</sup> anti-intrinsic factor<sup>24</sup> and ANCA.<sup>17</sup>

The presence of anti-idiotypic antibodies to ANCA in IVIG and in remission sera from patients with systemic vasculitis suggests a role for idiotypic regulation in the normal control of these disorders.<sup>17</sup> In antifactor VIIIc autoimmune disease, treatment with IVIG resulted in a dramatic and prolonged suppression of antibody, which was also demonstrated *in vitro*.<sup>25</sup> The recovery of patients post-IVIG was ascribed to the generation of anti-idiotypes against antifactor VIIIc antibodies.<sup>25</sup> In CU mediated by functionally significant autoantibodies, IVIG may provide anti-idiotypic antibodies capable of suppressing histamine releasing autoantibodies. IVIG represents an important therapeutic option in patients with severe, treatment resistant, anti-Fc $\epsilon$ R1 antibody-positive CU.

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