




# Resistant Chronic Spontaneous Urticaria – A Case Series Narrative Review of Treatment Options

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## Abstract

**Background:** Chronic spontaneous urticaria (CSU) can be extremely debilitating to the patient and challenging for the treating clinician. The National Institute of Health and Clinical Excellence (NICE) in the United Kingdom (UK) recommendation of omalizumab for patients who fail to respond to high-dose anti-histamines has improved treatment options and quality of life. However, there is still lack of clear guidelines for treatment of patients resistant to standard and anti-IgE therapies.

**Methods:** We discuss the therapeutic strategies employed among nine extremely resistant CSU cases and the heterogeneity between guidelines from different societies.

**Results:** Patients with anti-histamine-resistant urticaria either remained on omalizumab or started on immunosuppressive drugs (dapsons or ciclosporin) when they stopped responding to omalizumab. We used clinical assessment, skin biopsies (when available) and previous published reports to consider dapsons (for predominantly neutrophilic infiltration), or ciclosporin at doses between 2 and 4 mg/kg/day. One patient with ciclosporin-resistant urticaria responded to mycophenolate mofetil. Two patients remain on long-term omalizumab due to its relative safety and efficacy including 1 patient with underlying antibody deficiency where omalizumab was preferred over risks of using immunosuppressive medications.

**Conclusions:** These case studies bring to light the real-world difficulties in managing patients with resistant CSU and the need for generating the evidence base on alternative therapeutic options such as synergistic use of biologics and immunosuppressive drugs.

## Keywords

Chronic spontaneous urticaria, omalizumab, resistant urticaria, immunosuppressive drugs

## Background

Chronic spontaneous urticaria (CSU) is characterised by recurrent red, itchy cutaneous weals with central clearing, lasting for more than 6 weeks without a definite trigger. It is now well recognised that CSU forms a part of the urticarial group of disorders, which are associated with distinct skin reaction pattern with/without angioedema. Release of histamine and pro-inflammatory mediators from skin mast cells and basophils after IgE binds to its high-affinity receptor (FcεRIα) is considered the principal mechanism in CSU, but understanding the roles of autoantibodies, coagulation proteins (D-dimer) or the presence of distinct cell populations (such as eosinophils or monocytes or Th2 lymphocytes or neutrophils) on skin biopsies may provide clues into resistant CSU.<sup>1</sup>

A detailed clinical history and physical examination remains the cornerstone in the diagnosis of urticaria, together

with a few supportive investigations that may suggest probable autoimmune or infectious aetiology. Urticaria activity

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score (UAS) is often used to assess disease activity whereby a score of 0 (no activity) to 3 (intense activity) for each of the 2 urticaria symptoms (weals and pruritis) and weekly score, UAS7, helps to identify the severity (0-6, well-controlled; 7-15, mild, 16-27, moderate and 28-42, severe). The other criteria to assess disease activity is the urticaria control test (UCT) which sums the score between 0 and 4 for four questions, with lower scores suggesting more disease activity. The Dermatology Quality of Life Index (DQLI) 10-item score provides an overall assessment of disease burden.<sup>2-4</sup>

As standard doses of anti-histamines are often ineffective in treating CSU, up to four times the standard dose is recommended. In about 40% of patients with severe CSU, high-dose anti-histamines remain ineffective and these patients are considered non-responders.<sup>4,5</sup> In patients with an autoimmune basis for the cellular infiltrate, treatment with immunomodulators or a trial of humanised anti-IgE therapy (omalizumab) is generally considered to be safe and effective.<sup>6</sup> Studies have found up to half of patients with chronic urticaria may have an IgG or IgE antibody directed against the alpha subunit of the high-affinity IgE receptor (FcεR1α) which is believed to be the pathophysiological basis of autoimmune urticaria, including other autoantigens.<sup>7</sup> The role of anti-thyroid antibodies and response to omalizumab remains unclear even when thyroid disease is uniformly distributed among specific subgroups of CSU patients with different IgE levels.<sup>8</sup> Guidelines from the National Institute of Health and Clinical Excellence (NICE) in the United Kingdom (UK) recommend use of omalizumab for patients who failed high-dose anti-histamines, but UAS7 scores need to be reviewed at fourth dose and stopped if this has made no difference.<sup>9</sup> We have previously reported frequent relapses of urticaria when anti-IgE therapy is stopped necessitating further courses,<sup>10</sup> and there remains a paucity of treatment guidelines for such patients.<sup>5</sup> Moreover, clinicians have few evidence-based options when urticaria fails to respond to high-dose anti-histamines and anti-IgE therapy especially as alternatives to immunosuppression such as leukotriene receptor antagonist (eg, montelukast) or rupatadine are no longer included in recent expert recommendations.

In patients with urticaria resistant to high-dose anti-histamines and omalizumab, many clinicians resort to established immunomodulatory agents such as dapsone or ciclosporin. Dapsone (4,4'-diaminodiphenylsulfone) is the drug of choice in pure neutrophilic dermatoses by inhibiting neutrophil chemotaxis (such as in subcorneal pustular dermatosis),<sup>11</sup> and effective in a subset of patients with urticaria, but no clinical or laboratory markers for dapsone responsiveness in CSU have been identified. Ciclosporin works by selectively blocking calcineurin, and has been extensively used in Dermatology to treat atopic eczema/dermatitis and psoriasis resistant to topical therapies.<sup>12</sup> Other immunomodulatory medications such as colchicine, methotrexate or anti-interleukin-1 (IL-1) have been used for specific diagnoses such as resistant neutrophilic dermatoses, paraprotein-related urticarias

(Schnitzler syndrome) or inherited fever syndromes with rashes such as familial Mediterranean fever.<sup>13</sup> However, justifying use of methotrexate or obtaining funding for anti-IL-1 therapies for resistant CSU alone can be particularly difficult.

Studies focusing on skin biopsy samples estimate that in 4-18% of urticaria, the skin infiltrates are neutrophil predominant (termed as neutrophilic urticaria), but some cases show significant eosinophil and mononuclear cell infiltrates with more marked vasodilatation and endothelial swelling.<sup>14</sup> The clinical features of neutrophilic urticaria are not typical of conventional urticaria: the lesions are more painful/burning than pruritic, and usually unresponsive to anti-histamines. The pathogenic mechanism may be similar to the neutrophilic urticarial dermatoses involving the inflammasome pathway, and lack of response to anti-histamines supports this pathologic process. Since all currently approved CSU therapies target either IgE or mast cells, it is worth considering the role of different treatment modalities in selected patients. The timing (and possibly location of skin biopsies) and concomitant treatments may affect the cellular infiltrate in CSU. Hence, this diagnostic modality is not a practical approach in clinical trials, and therefore remains difficult to understand specific CSU subgroups at the cellular level.

In this case series, we have tried to summarise our experience of different treatment strategies employed in patients with resistant CSU as dictated by varying clinical situations (ie, co-morbidities, needle phobia preventing anti-IgE therapy, patient preferences on immunosuppressive drugs and avoiding treatment complications) and hence may not adhere to international guidelines. We discuss the advantages of some strategies but acknowledge the absence of a strong clinical evidence base.

In particular, these complex cases have enabled a discussion of:

- The management of CSU patients where anti-IgE therapies are either ineffective, not tolerated, or not acceptable to patients
- The extent to which current national and international CSU guidelines address these clinical situations
- The potential role of skin biopsy in resistant CSU
- Multidisciplinary approaches to management and treatment options for this category of patients
- The need for patients to be informed of the remitting relapsing nature of the disease, particularly when resistant to biologics or even when there is good initial response to biologics

## Methods

This is a narrative review of 9 patients with refractory CSU who failed to respond to high doses of anti-histamines (×4 standard dose) and some required to frequently use oral corticosteroids to control severe relapses. None of the patients had evidence of inducible/physical urticaria and no suggestion of active or previous diagnosis of systemic or cutaneous lupus erythematosus (SLE or CLE).

All patients were followed up at the respective Immunology clinics for several months, and patients consented for skin biopsy as part of routine clinical care when there was no response to conventional therapy. Direct immunofluorescence or split-skin studies and biopsy of non-lesional skin were not performed. Mast cell numbers were reported in some patients, to exclude mastocytosis.

Patients were counselled to receive immunomodulatory therapy as dictated by clinical need and where benefits outweighed risks. Patients were regularly monitoring as per pharmacovigilance requirements for all immunosuppressive drugs. Glucose-6-phosphate dehydrogenase (G6PD) level/activity were checked in all patients before initiation of dapson therapy (qualitative assay reported as 'positive' if present or 'deficient', tested on the lateral flow colorimetric test platform between 18 and 25 °C).

All patients consented for their case history and treatment details to be published. No ethical approval was required as this was not a research project, and investigations were undertaken solely according to clinical requirements.

No statistical analyses were involved in the interpretation of test results.

## Case Studies

### Patient 1

A 56-year-old woman of Indian origin presented with features of CSU for 11 years with a background history of severe persistent allergic rhinitis. Her CSU symptoms remained uncontrolled on fexofenadine 180 mg twice daily, cetirizine 10 mg twice daily. Montelukast 10 mg once at night did not improve her symptoms after 10 weeks and she discontinued this treatment (investigations are outlined in Table 1). Skin biopsy was done when she was on twice daily Fexofenadine 180 mg and cetirizine 10 mg including montelukast 10 mg once at night.

She was not keen to start anti-IgE therapy but agreed to a trial of dapson. G6PD (qualitative assay) level was normal and she was started on 100 mg once daily. Pre-dapson UAS7 score was 28 that reduced to 10 within 3 weeks. UAS7 score was 0 at 6 weeks and remained <6 for 4 months, when dapson was stopped. She had a relapse within 2 months of stopping (UAS7 = 30), and required dapson for another 5 months. Since then, she has remained in remission only on fexofenadine 180 mg twice daily for the past 2 years.

### Patient 2

A 60-year-old woman with underlying type 2 diabetes mellitus, hypothyroidism and hypertension developed severe CSU for 2 years that had responded only to steroid therapy. She required prednisolone 10-15 mg most days for more than 18 months, despite taking fexofenadine 720 mg/day and cetirizine 20 mg/day. She had a lesional skin biopsy that

showed no evidence of vasculitis (investigations outlined in Table 1). She kept having urticarial flare ups almost on daily even after 2 doses of omalizumab at 300 mg and refused further biologic therapy.

G6PD level (qualitative) was normal, and she started dapson at 100 mg once daily while on prednisolone 15 mg, fexofenadine and cetirizine. Pre-dapson UAS7 score was 16 that dropped to 0 in 4 weeks, allowing slow tapering and then stopping prednisolone. Dapson was stopped after 3 months, and she continued fexofenadine 180 mg twice daily. Unfortunately, she suffered a relapse of urticaria at 6 months (UAS7 = 42) and dapson was continued for a further year. At the last review, the urticaria was controlled on fexofenadine 180 mg once daily.

### Patient 3

A 44-year-old South Asian woman with underlying hypothyroidism, vitiligo and hyperlipidaemia had developed urticaria resistant to multiple anti-histamines and only responsive to steroids. She had been on continuous steroids for almost 2 years until review in the Immunology clinic. By this time, she had developed steroid-induced diabetes mellitus and hypertension. She was on metformin 1 g twice daily, levothyroxine 100 µg, ramipril 2.5 mg, fexofenadine 720 mg/day, hydroxyzine 50 mg, cetirizine 10 mg, prednisolone 10 mg once daily. Her median UAS7 score over past 12 weeks was 22 (range, 16-28). She had 2 hospital admissions for hyperglycaemia-requiring sliding scale insulin that was very stressful for her as she was needle phobic.

She underwent a skin biopsy (UAS7 score 28) that showed no features of vasculitis (investigations outlined in Table 1). Due to severe needle phobia, she refused omalizumab therapy.

Dapson at 100 mg once daily was started, but in the first 6 weeks she required 2 courses of oral steroids (15 days each). By 10 weeks of dapson therapy, her UAS7 scores were persistently less than 10. By 3 months, UAS7 was 6 and dapson was continued for 5 months. However, she then stopped dapson after experiencing a variety of symptoms such as loss in appetite, headaches, dizziness and the urticaria had relapsed (UAS7 > 28). She then agreed to start ciclosporin at 50 mg twice daily (2 mg/kg/day) that controlled the urticaria (UAS7 10 at month 4). By 6 months, the dose had reduced to 25 mg twice daily that she continued for a further 6 months. The urticaria has remained in partial remission on regular fexofenadine and cetirizine (at standard doses) with occasional minor flares that respond well to high-dose anti-histamines.

### Patient 4

A 58-year-old Caucasian man had severe CSU requiring almost continuous steroids for 5 months. He was on treatment for essential hypertension, hyperlipidaemia and thyroxine

Table 1. Overview of Cases.

Patient details	Duration of CSU	Underlying medical problems	Relevant laboratory findings	Skin biopsy features	Response to omalizumab/other drugs	Current status
P1 56/ Female Asian Indian	11 years	Severe persistent allergic rhinitis	ANA 2+ (1 in 80) IgE 1179 kU/L SpIgE Dp 73.8 kU/L SpIgE Df >100 kU/L Mast cell tryptase <1 ng/L Anti-TPO, TG – negative G6PD screen – normal	Mild dermal oedema with neutrophilic predominance, no features of vasculitis	Omalizumab not tried – patient preference	Dapsone 100 mg (about 9 months), urticaria controlled on high-dose anti-histamines only (at last review, pre-pandemic)
P2 60/ Female Asian Indian	25 years (intermittent episodic), 2 years (severe)	Type 2 diabetes mellitus Hypothyroidism Hypertension	Anti-TPO, TG – positive G6PD screen – normal	Dermal oedema with predominantly perivascular neutrophilic infiltrate, but no features of vasculitis	Relapse of urticaria after both first and second doses of omalizumab – stopped	Dapsone 100 mg (around 18 months), urticaria controlled on anti-histamines only (at last review pre-pandemic)
P3 44/ Female South Asian	2 years	Hypothyroidism Vitiligo Hyperlipidaemia Steroid-induced diabetes mellitus Hypertension	ANA 1+ (cytoplasmic pattern) Anti-TPO, TG – positive G6PD level – 11.4 U/gHb (reference range, 4.6-13.5) Positive anti-TPO at 374 U/ml (ref range <35 U/ml) IgE 26 U/ml G6PD screen – normal Complement C3 1.3 g/L and C4 at 0.12 g/L	Dermal oedema with mixture of perivascular neutrophilic and lymphocytic infiltrate, but no features of vasculitis Not done	Omalizumab not tried – patient preference (needle phobia) Intolerant to dapsone after initial response	Ciclosporin (1 year), urticaria controlled on anti-histamines only (at last review pre-pandemic)
P4 58/Male British	1.5 years	Essential hypertension Hyperlipidaemia Steroid-induced diabetes mellitus Hypothyroidism	Positive anti-TPO at 374 U/ml (ref range <35 U/ml) IgE 26 U/ml G6PD screen – normal Complement C3 1.3 g/L and C4 at 0.12 g/L	Not done	Omalizumab (4 doses) – no response Dapsone-induced oxidative haemolysis (see Table 2)	Urticaria controlled on ciclosporin (18 months+)
P5 43/Male Caucasian	3 years	Type 2 diabetes on insulin Hypertension Hyperlipidaemia	N/A	Not done	Omalizumab (4 doses) – no response Ciclosporin – no response (including rise in serum creatinine)	Urticaria controlled on Mycophenolate mofetil 3 g daily dose
P6 33/ Female Caucasian	>1 year	Intermittent episodic urticaria	HR-Urticaria test 25% (RefLab, Denmark; positive histamine release >16.5%)	Not done	2 cycles of omalizumab (6 doses each cycle) with 3 months of remission between cycles	Not keen on immunosuppressive therapies; urticaria controlled on anti-histamines and intermittent steroids during severe relapses
P7 25/ Female Caucasian	2-3 years (intermittent)	Common variable immunodeficiency on IgRT	IgE <2 kU/L	Not done	Omalizumab 300 mg every 4 weeks (2 cycles) – urticaria controlled	Increased frequency of omalizumab being considered
P8 28/ Female Caucasian	8 years	Hypothyroidism Polycystic ovary syndrome Anxiety and depression	Anti-TPO 236 IU/ml (normal<35 IU/ml); Anti-TG – negative G6PD screen – normal	Moderate dermal oedema with perivascular neutrophilic infiltrates, but no features of vasculitis	Omalizumab (4 doses) – no response	Dapsone 100 mg (around a year), urticaria controlled on anti-histamines only
P9 49/ Female Caucasian	7 years	Type 2 diabetes Hypertension Hyperlipidaemia Anxiety	G6PD screen – normal	Dermal oedema and perivascular neutrophilic infiltrate but no features of vasculitis	Omalizumab response eventually faded after 2 years Dapsone-related hepatic and haematologic toxicity	Urticaria controlled on ciclosporin & high-dose anti-histamines

Abbreviations: ANA, anti-nuclear antibody; IgE, immunoglobulin E; spIgE, specific IgE; TPO, thyroid peroxidase; TG, thyroglobulin; Dp, dermatophagoides farinae; G6PD, glucose-6-phosphate dehydrogenase; HR, histamine release; IgRT, immunoglobulin replacement therapy; N/A, not available.

supplementation for autoimmune hypothyroidism. At the time of review with Immunology, the duration of urticaria had exceeded 18 months (median UAS7 score 32). He had minimal response to fexofenadine (total 720 mg/day), rupatadine 10 mg three times a day, hydroxyzine 50 mg and montelukast 10 mg including prednisolone doses between 15 and 20 mg daily (investigations outlined in Table 1).

Omalizumab 300 mg subcutaneously (s/c) every 4 weeks made little difference to the urticaria and he was unable to stop oral steroids even after 4 months into omalizumab therapy (lowest UAS7 score was 16 on 10 mg oral prednisolone). He decided against higher dose of omalizumab injections and opted for a trial of dapson. With underlying hypertension, hyperlipidaemia and normal G6PD screen, dapson was considered a safer option than ciclosporin. However, within 4 weeks of starting dapson, he complained of fatigue and within 6 weeks he was clinically jaundiced with abnormal biochemical parameters. Blood film showed polychromasia and numerous bite cells (degmacytes), with decreasing haemoglobin, rise in bilirubin and absent haptoglobin. Dapson-related oxidative haemolysis was considered highly likely, and stopped immediately. Steroids were re-started to control the urticaria.

Within a week of stopping dapson, haemoglobin improved with fall in bilirubin level and disappearance of bite cells from blood films. With frequent requirement of steroids, he developed diabetes. The urticaria was finally controlled on high-dose anti-histamines (fexofenadine 720 mg/day, cetirizine 20 mg/day, hydroxyzine 25 mg at night) and ciclosporin 75 mg twice daily (2 mg/kg/day) with metformin 500 mg twice daily and careful blood glucose monitoring. He had a flare up when ciclosporin was lowered to 25 mg twice daily after 6 months, but again responded on 75 mg twice daily. At last follow-up since starting ciclosporin almost 2 years ago, he had only 1 significant flare up requiring a short course of steroids and remains on ciclosporin 25 mg twice daily. Minor relapses respond well to low-dose anti-histamines only.

### **Patient 5**

A 43-year-old Caucasian man with a 3-year history of CSU failed to respond to fexofenadine 720 mg/day, montelukast 10 mg once daily and required frequent short rescue courses of prednisolone. Past medical history included type 2 diabetes on insulin, hypertension on candesartan, hyperlipidaemia on simvastatin and aspirin. After commencing omalizumab 300 mg s/c 4 weekly, his symptoms completely resolved within the first 2 months but the urticaria relapsed requiring further prednisolone, but then failed to respond to subsequent doses of omalizumab.

Ciclosporin at a dose of 2 mg/kg twice daily completely resolved the symptoms and the dose gradually reduced to 0.5 mg/kg twice daily. At that dose, the symptoms recurred and were requiring dose adjustment to 0.75 mg/kg twice

daily, which controlled the urticaria for approximately 2 years. However, he still had frequent relapses that responded only to prednisolone. With increasing creatinine levels, he was switched to mycophenolate mofetil (urticaria in remission at 3 g daily dose).

### **Patient 6**

A 33-year-old Caucasian woman with CSU required up to 60 mg of prednisolone (with slow tapering) in addition to loratadine 40 mg/day, ranitidine 150 mg twice daily and montelukast 10 mg once daily to control the breakthrough eruptions. She had a previous history of urticaria 8 years ago (that lasted a year) and required high-dose anti-histamines, ranitidine and montelukast, as well as intermittent courses of steroids (investigations outlined in Table 1).

Prednisolone was gradually reduced but suffered relapses and was commenced on omalizumab 300 mg s/c every 4 weeks. The symptoms started improving after the fourth dose of omalizumab (prednisolone stopped) and completely resolved after the sixth dose. She had remission of her symptoms for 3 months after the first cycle (6 doses) but relapsed within 4-6 weeks, and remains on third cycle of omalizumab. However, she has continued to require low-dose steroids between injections, and treatment with ciclosporin was discussed with the patient. However, due to the risk of immunosuppression and monitoring requirements during in the COVID-19 pandemic, the patient was not keen on this treatment option.

### **Patient 7**

A 25-year-old Caucasian lady was under Immunology review since diagnosis of common variable immune deficiency (CVID) at the age of 20 years (presented with severe hypogammaglobulinaemia): IgG 2 g/L (normal range 6-16 g/L), IgA <0.02 g/L, IgM at 0.20 g/L (normal range 0.5-2.0 g/L). Vaccine responses (antibody titres post-vaccination) were poor and lymphocyte immunophenotyping showed normal lymphocyte subsets but absent (<1%) switched memory B-cells. She remained very well on home subcutaneous (self-administered) immunoglobulin replacement therapy (IgRT), with no breakthrough infections. There was no CT evidence of bronchiectasis, lymphadenopathy or organomegaly.

She was also noted to have vitiligo, and developed skin rashes that were consistent with CSU. Routine biochemical and haematologic parameters were normal. Total IgE level was undetectable <2 kU/L. Trough IgG levels remained excellent between 8 and 9 g/L (except during pregnancy), and she remained well with no infections. IgM was noted to normalise more recently, while IgA remains undetectable. Autoimmune serological tests (thyroid antibody or anti-nuclear screen) were not undertaken as this is unreliable when receiving IgRT.

Her CSU symptoms responded only partially to high-dose anti-histamines and the progressive severity of her symptoms justified starting omalizumab 300 mg every 4 weeks, with a good initial response to therapy. This therapy has needed to be continued over 12 months. However she later developed persistent symptoms despite omalizumab and high-dose anti-histamines. She is under constant review with both Dermatology and Immunology teams and currently on a trial of more frequent of omalizumab dosing at 300 mg every 2-3 weeks. Skin biopsy has not been done, but remains under consideration.

### Patient 8

A 28-year-old Caucasian woman presented with features of CSU for 8 years that worsened over the last 2 years. She was treated with fexofenadine 360 mg twice daily and montelukast 10 mg once daily but remained symptomatic, which required treatment with short courses of prednisolone every other week. She had a background history of hypothyroidism, polycystic ovary syndrome, anxiety and depression and was on levo-thyroxine 100 mcg, metformin 500 mg twice daily, sertraline 50 mg daily. Investigations are outlined in Table 1.

UAS7 scores over 6 weeks remained between 36 and 40 and she was commenced on omalizumab 300 mg every 4 weeks. Her symptoms completely resolved in the first 2 months while she was on omalizumab, but within 1-2 weeks after the third and fourth doses of omalizumab, the urticaria relapsed and required further courses of prednisolone. In total, she had four doses of omalizumab which made no overall difference to the urticaria.

G6PD (qualitative assay) level was normal and she was started on dapsone 100 mg once daily. Her UAS7 scores significantly improved by 3-4 weeks (UAS7 score between 6 and 8) and by 10 weeks, UAS7 score was between 2 and 4, suggesting excellent control. Urticaria was in remission after 8 months, when dapsone was stopped. She had a relapse within 2 months of stopping (UAS7 = 34) and stayed on dapsone for another 4 months. Since then, she has remained in remission requiring only fexofenadine 180 mg once/twice daily for the past 10 months.

### Patient 9

A 49-year-old Caucasian woman presented with features of CSU for about 7 years. She was on fexofenadine 360 mg twice daily and montelukast 10 mg once daily but was getting frequent breakthrough episodes. She had a background history of type 2 diabetes, hypertension, hyperlipidaemia and anxiety, and was on metformin 1 g twice daily, ramipril 5 mg, rosuvastatin 20 mg, aspirin 75 mg and sertraline 50 mg once daily.

Skin biopsy showed dermal oedema and a perivascular neutrophilic infiltrate but no features of vasculitis. UAS7

score was 34-36 when she was commenced on omalizumab 300 mg every 4 weeks. This treatment proved extremely effective but required four cycles almost on a continuous basis to remain in remission (total duration of omalizumab >2 years). However, the urticaria relapsed and further courses of omalizumab and high-dose anti-histamines were ineffective.

G6PD (qualitative assay) level was normal and she was started on dapsone 100 mg once daily. However, within 2-3 weeks of starting dapsone, she complained of gastrointestinal (GI) symptoms (nausea, intermittent diarrhoea) and fatigue. After 5 weeks of dapsone therapy, she developed jaundice with highly elevated liver enzymes (ALT 296 U/l, AST 112 U/l), raised bilirubin at 48 mg/dl and methaemoglobinemia. Dapsone was stopped immediately and she required a short course of steroids to control the urticaria. Within a few weeks her liver enzymes, bilirubin and haemoglobin had normalised.

However, her urticaria flared up again and because of her diabetes, steroids could not be continued. Ciclosporin 75 mg twice daily (2 mg/kg/day) was commenced along with fexofenadine 360 mg twice daily with improvement. Within the last 6 months her symptoms have been under good control and ciclosporin at 50 mg once daily together with fexofenadine 180 mg twice daily has controlled her urticaria.

## Discussion

These cases provide a real-world glimpse of the difficulties clinicians face when choosing treatment options in CSU patients who do not respond to high-dose anti-histamines and anti-IgE biologic therapy. It also shows the significant impact of CSU on patient's quality of life with regards to lost hours at work, multiple hospital visits, including admissions to Emergency Department, costs of therapy and psychosocial issues. The majority of patients with resistant CSU in this case series required oral steroids to control relapses. Chronic long-term steroid use makes it difficult to assess disease severity and its effects on skin biopsy. Recurrent courses of steroids required to control severe disease also added to patient anxiety about steroid dependence, side effects including steroid-induced diabetes (as noted in patients P3 and P4), cataracts and mood disorders.

In many countries including the UK, omalizumab is the only approved treatment for anti-histamine-refractory CSU. However, about 30% of patients remain symptomatic at licenced doses of omalizumab 150 and 300 mg, even after a treatment period of over 6 months.<sup>15</sup> In recent years, there have been several studies on up dosing of omalizumab in CSU patients who do not respond or partially respond to 300 mg of omalizumab after 3-6 months of treatment, suggesting a stepwise approach using 450 mg and then up dosing to 600 mg.<sup>15,16</sup> Low total IgE has been considered as a factor towards omalizumab non-responsiveness

(example, in patients with antibody deficiency as in patient 7) and may predict requirement of special protocols.<sup>17,18</sup>

The UK NICE guidance in CSU states that omalizumab should be stopped at or before the fourth dose if the condition has not responded, and funding for this biologic medication is contingent on this guidance being followed.<sup>9</sup> However, Kaplan et al. suggest that patients should be treated for at least 6 months before being considered as omalizumab non-responders.<sup>19</sup> In the ASTERIA I study, 58% of patients in the omalizumab group who did not achieve a UAS7  $\leq 6$  by week 12, did so subsequently during weeks 13-24.<sup>20</sup>

The presence of a positive basophil histamine release assay (BHRA) has been linked to worse response to anti-IgE therapy, and better response to ciclosporin and fenebrutinib.<sup>21</sup> Unfortunately, this assay is not universally available at hospitals in the UK, and requires shipping overseas. Hence, we do not have routine clinical results for BHRA on all patients and are unable to comment on the potential role of this assay in determining response to anti-IgE therapy. In 4 of 9 patients, thyroid autoantibodies (TPO and/or TG antibodies) were positive. These antibodies have been considered a potential marker for autoimmune urticaria. Two of 4 patients with TPO/TG antibodies responded to ciclosporin, and the others to dapsons. As there is only a modest relationship between these antibodies and BHRA, the former cannot be used as a direct substitute.<sup>22</sup> We have summarised in Table 2 the possible factors influencing or suggestive of inadequate clinical response to therapy in CSU.<sup>23-25</sup> Controversy remains as to whether eosinophil modulation is another mechanism of action of omalizumab in urticaria.<sup>26-28</sup>

We noted that 4 patients who started dapsons had excellent control of urticaria within 3-10 weeks, though 1 patient with clinical response needed to discontinue due to intolerance. Two other patients developed haematologic toxicity (one also developed hepatotoxicity) within 4-6 weeks. In the clinical responders, the effect was not sustained in

the long-term. Of the responders, 2 patients were ANA positive (although most likely non-specific at the titres and type of staining noted) and 3 patients were positive for anti-thyroid antibodies. None of the patients had evidence of underlying systemic inflammatory disease to be classed as neutrophilic dermatoses especially where skin biopsies were suggestive of neutrophilic urticaria, although this probably signifies an inflammatory component of the urticaria.<sup>29</sup> This also applies to patient 7, where the urticaria could be considered as a part of autoimmune dysregulation in CVID, akin to the vitiligo. Furthermore, there are practical problems in exposing patients with genetically unknown primary immune deficiency disorders (CVID being an example) to further immunosuppressive therapy with additional risks around infections and malignancy.

Patients who stopped dapsons after achieving remission relapsed at several time points requiring further courses of dapsons, and they continue to remain on anti-histamines only. Due to the small number of cases, no conclusions regarding clinical or laboratory features that could determine dapsons responsiveness were identified. Although patients had evidence of neutrophilic predominance on active urticarial skin biopsy specimens, they did not have any other features of systemic inflammation. This is in line with Martins et al. who considered that neutrophilic urticaria is probably not a distinct entity in the absence of systemic symptoms.<sup>29</sup> Amin et al. undertook a retrospective longitudinal chart review of 221 patients where they noted 34 patients with neutrophil predominance on skin biopsy had poorly controlled urticaria, but with a high odds ratio of dapsons response [adjusted odds ratio 5.4 (3.2-9.1)], while lymphocyte- or eosinophil-predominant urticaria were well-controlled with just standard treatment.<sup>30</sup>

The treatment options used in our case series resemble those reported by Criado et al. where they treated 22 CSU patients based on type of cell infiltrate in skin biopsy: (mixed cellular infiltrate or neutrophil predominance) with

**Table 2.** Factors Influencing Clinical Response in CSU.

Factors	Example
Associated clinical features	Vasculitis-like features Presence of physical urticaria / dermographism Angioedema more pronounced than urticaria <sup>6</sup>
High urticaria disease activity scores	High UAS7 suggest poor response to second-generation anti-histamines
C-reactive protein (CRP) D-dimer	High CRP and D-dimer may suggest poor response to second-generation anti-histamines
Serum total IgE level	Low total IgE may suggest poorer response to omalizumab
Autoimmune basis	Presence of autoantibodies (eg, thyroid antibodies, anti-nuclear antibody) or other autoimmune diagnoses
Basophil histamine release assay (BHRA) or histamine-releasing antibodies	Positive BHRA may suggest poorer response to omalizumab; better response to ciclosporin
Skin biopsy findings	Neutrophilic urticaria may suggest better response to dapsons/colchicine <sup>25</sup>
Inappropriate dosing or dose frequency	Trials of higher dose or higher frequency omalizumab in progress
Insufficient duration of treatment	May consider $\geq 6$ months omalizumab before labelling as non-responder
Suboptimal patient adherence	To oral medication, or attendance for omalizumab injections

either anti-histamines/dapsone (class A), neutrophil predominance (class B) with colchicine only, eosinophilic predominance (class C) with montelukast only.<sup>31</sup> Four patients in class A, 11 in class B and 7 in class C showed complete remission (time to remission 30-90 days, mean  $46.84 \pm 20.76$ ) while 1 patient in class B and 2 in class C did not respond to treatment. Whereas 16 patients remained in remission at 2 years, 3 patients had relapsed (one in each class) and 2 responded to treatment. The authors concluded that dapsone or colchicine might be their therapeutic choice in presence of intense neutrophilic infiltrates, while montelukast may be the choice if eosinophilic infiltrates were the predominant finding on lesional skin biopsy. In this subgroup of CSU patients with eosinophilic infiltrates (not otherwise candidates for montelukast), dapsone could be tried as it appears effective in eosinophilic cellulitis (Well's syndrome).

Gusdorf et al. described 5 of 7 lupus patients (all female, aged 13-45 years) with neutrophilic urticarial dermatoses who responded to dapsone or colchicine therapy.<sup>32</sup> Standard lupus medications (immunosuppressive drugs) such as prednisone, hydroxychloroquine, mycophenolate mofetil, and methotrexate were not effective on the skin lesions. Anti-histamines were effective in only one patient while dapsone or colchicine was effective in 5 patients. While this study cannot be directly extrapolated onto CSU patients, it is certainly possible that the finding of neutrophilic infiltrate in skin lesions may indicate a feature of underlying systemic inflammation that may not be obvious in all cases. It is therefore worthwhile considering skin biopsy in patients with resistant CSU but more importantly in those who experience any systemic inflammatory symptoms

(with or without neutrophil predominant urticaria) where dapsone can be particularly effective.

Our previous report on montelukast as added-therapy to H1 and H2 anti-histamines showed that it was effective in controlling the urticaria in about 50% of patients. However, none of our patients in the report had skin biopsies to correlate with this finding, and we were unable to find any specific clinical features or laboratory findings that could predict a response to montelukast.<sup>33</sup> It is also interesting to note that the European Academy of Allergy and Clinical Immunology (EAACI) has called for further research with controlled multi-centre trials on the possible therapeutic effect of addition of anti-H2 blockers, montelukast and sulfones such as dapsone among others.<sup>5</sup> This would help better characterise whether a subgroup of patients may respond to a specific combination of drugs using the concept of synergistic multi-drug therapy as used for malignancies, human immunodeficiency virus infection (HIV) and tuberculosis.<sup>34</sup> Garbayo-Salmóns and colleagues report the usefulness of methotrexate combined with omalizumab,<sup>35</sup> similar to Maoz-Segal and colleagues report on 'intensified protocol' in 18 of 289 resistant CSU using combinations of omalizumab and ciclosporin ( $n = 16$ ), methotrexate ( $n = 1$ ) and azathioprine ( $n = 1$ ) where 14/18 (78%) achieved complete remission.<sup>26</sup> Prospective data of resistant CSU cases collected as part of national registries can also be a powerful tool towards generating an evidence base of non-conventional drug regimens outside of clinical trials.<sup>36</sup>

In Table 3, we have summarised and compared the guidance for management of CSU unresponsive to high-dose anti-histamines and anti-IgE therapy from various national and international organisations. The AAAAI endorsement

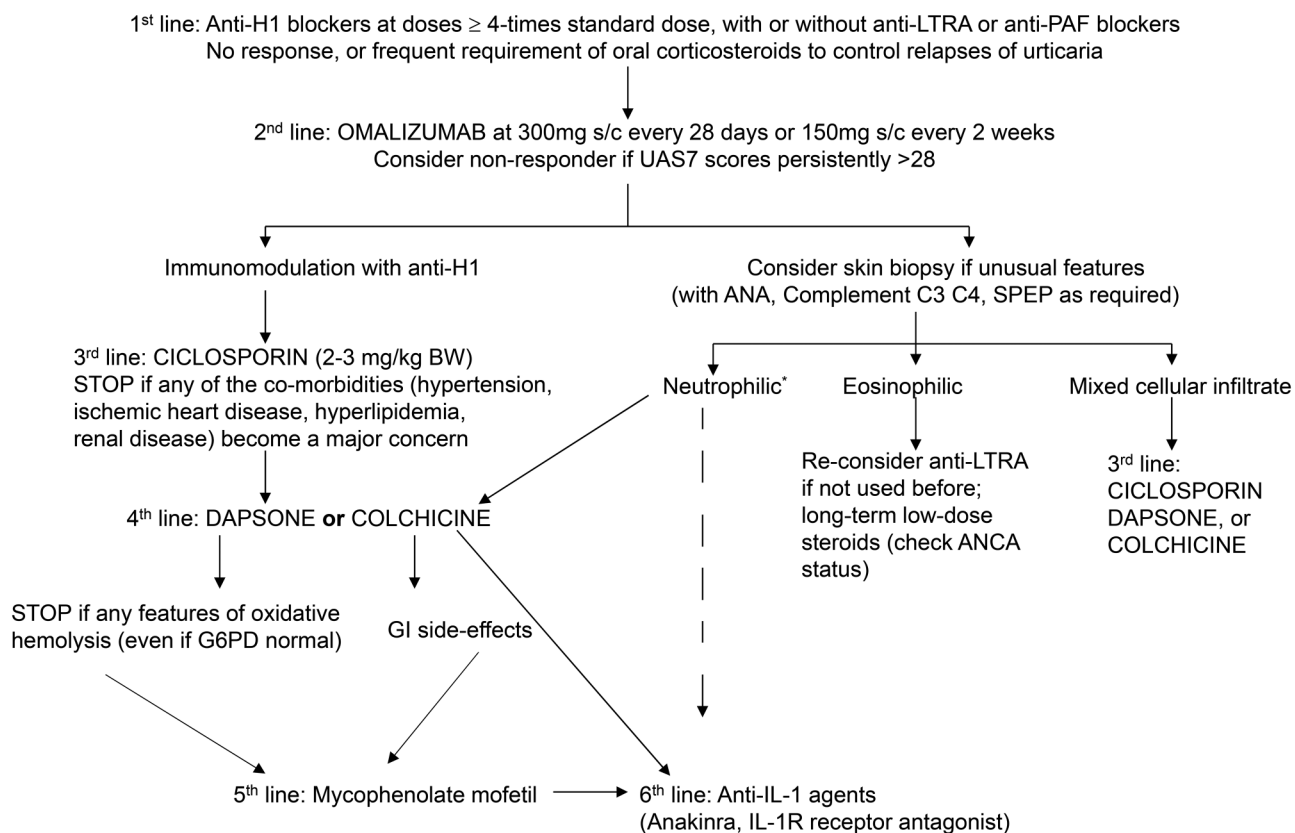
**Table 3.** Comparison of CSU Treatment Options Among Different Societies.

Treatment options	EAACI/GA <sup>2</sup> LEN/EuroGuiDerm/APAAACI	BAD	ASCIA (New Zealand)	ASCIA (Australia)
Second line	Omalizumab 300 mg every 4 weeks for at least 6 doses. If not effective, then: higher doses of omalizumab and/or shorter dose interval (off-label use)	Ciclosporin <b>or</b> omalizumab	Ciclosporin	Short-term trial of montelukast <b>OR</b> Omalizumab 300 mg monthly for 6 months
Third line	Ciclosporin 3.5-5 mg/kg/day	Ciclosporin <b>or</b> omalizumab	Omalizumab	Ciclosporin
Fourth line	Doxepin, interferon, IVIG, methotrexate, montelukast, mycophenolate mofetil, NB-UBV, plasmapheresis, sulfasalazine (Listed in alphabetical order)	Azathioprine, dapsone, doxepin, hydroxychloroquine, IVIG, methotrexate, mycophenolate mofetil, NB-UBV, sulfasalazine, oral tacrolimus (listed in alphabetical order)		
Further notes	H2 antagonists and dapsone now considered to low evidence base	Consider testing serum total IgE and basophil histamine release assay in CSU not responding to first line treatment ( $\times 4$ sgAH)		Ranitidine and doxepin no longer recommended.

APAAACI = Asia Pacific Association of Allergy, Asthma, and Clinical Immunology; BAD = British Association of Dermatologists; EAACI = European Academy of Allergology and Clinical Immunology; EuroGuiDerm = Guidelines from European Dermatology Forum; GA<sup>2</sup>LEN = Global asthma and allergy European network; IVIG = intravenous immunoglobulin; NB-UBV = narrow-band ultra-violet phototherapy;  $\times 4$ sgAH, 4 times standard dose second-generation anti-histamines (additional ref: Allergy. 2022 Jan 20. Ahead of print doi: 10.1111/all.15227).



## Resistant CSU



\* Neutrophilic urticarial dermatoses is a distinct entity that frequently responds to dapstone (inhibits neutrophil migration), with colchicine and finally anakinra reserved for resistant NUD

**Figure 1.** Flow-chart outlining the therapeutic options used for our patients with resistant CSU in this case series. \*Neutrophilic urticarial dermatoses are a distinct entity and may respond to dapstone or colchicine, while Anakinra is reserved for autoinflammatory fever syndromes (cryopyrinopathies) or resistant cases of neutrophilic urticaria. Abbreviations: CSU, chronic spontaneous urticaria; Anti-H1, anti-histamine; LTRA, leukotriene receptor antagonist; PAF, platelet activating factor; UAS7, urticaria activity score over 7 days; s/c, subcutaneous; ANA, anti-nuclear antibody; SPEP, serum protein electrophoresis; G6PD, glucose-6-phosphate dehydrogenase; ANCA, anti-neutrophil cytoplasmic antibody; GI, gastrointestinal; BW, body weight; IL-1, interleukin-1.

of the 2021 combined European and Asia-Pacific guideline also details possible options for CSU patients who fail high-dose anti-histamines and anti-IgE therapy. As might be expected, there is variation across the globe and newer publications continue to highlight on the heterogeneity between guidelines.<sup>37</sup> One particular finding is that several guidelines consider ciclosporin as an alternative to anti-IgE for CSU resistant to high-dose H1 anti-histamines and appears even above anti-IgE in the 2020 Australasian Society for Clinical Immunology & Allergy (ASCI) – New Zealand algorithm (though the ASCI have recently also endorsed the 2021 combined European & Asia-Pacific guideline where omalizumab precedes ciclosporin). We have also summarised our proposed treatment pathway for resistant CSU in Figure 1.

Our report has its limitations. Retrospective case descriptions are biased with choosing very difficult patients, universal treatment pathways were not followed and patients have

very different clinical backgrounds affecting choice of therapies (especially when it came to immunosuppressive medications). However, the report shows that most centres will have such patients and that treatment choices made may not be in agreement with other centres or guidelines proposed by various societies, but are not necessarily wrong decisions. These biases dictate the necessity of multi-centre study for unification of the diagnostic algorithm and optimisation of the individualised treatment approaches of severe CSU.

The future seems exciting for CSU management with second-generation anti-IgE antibody Ligelizumab<sup>38-40</sup> and omalizumab biosimilars have completed clinical studies in asthma<sup>41,42</sup> that may be available for CSU in other countries. Newer immunomodulatory agents currently being explored in clinical trials for CSU include dupilumab (anti-IL-4/IL-13 antagonist) given s/c every 2 weeks, and benralizumab (IL-5 inhibitor) given s/c every 8 weeks. Perhaps most

exciting would be success of the newer-generation BTK (Bruton tyrosine kinase) inhibitors such as remibrutinib (currently in Phase 2 clinical trials) that are once daily oral-based medications, but use may be limited due to cardiac side effects, bleeding and infection risks in some patients.<sup>43–45</sup> Promising novel agents in early-stage development include anti-thymic stromal lymphopoietin/TSLP (Tezepelumab), human IgGκ monoclonal antibody that binds and blocks C5a receptor 1 (avdoralimab) or the humanised nonfucosylated monoclonal antibody against sialic acid-binding Ig-like lectin 8 (Siglec-8) that improves eosinophil counts in eosinophilic GI diseases and also inhibits mast cell IgE-mediated degranulation.<sup>46,47</sup> Despite the range of potential new therapies, most are still within various (early) phases in clinical trials and will take a long time before they were on national guidelines for use in everyday clinical practice. Therefore, during this transition period alternative immunosuppressive agents are required for our resistant CSU patients.

With availability of specialised services among many centres in the UK but small patient cohorts, there remain many questions around the best clinical practice for these patients. For example, how should clinicians counsel patients around the long-term risks with use of immunosuppressants in CSU? When should we consider a skin biopsy? With highly variable clinical courses within individual patients, perhaps a more patient-centred and disease narrative approach to these patients' group may be more informative? For example, many specialists can see that prolonged courses of omalizumab appear effective in many patients, but defining optimal duration of such therapies (as required in some organisational prescribing set-ups) appears impossible to predict, and resource constraints may make these uncertainties more challenging to account for financially.

## Conclusion

This small case series highlights the major gaps in our understanding and approaches in managing patients with resistant CSU. Guidelines from larger societies, beyond omalizumab and ciclosporin, do not outline specific treatment or investigation strategies to aid clinicians managing this complex group of patients. Apart from data supporting ciclosporin efficacy, there is very limited data for other immunosuppressants when omalizumab fails in clinical practice. In selected patients, synergistic biologic and immunosuppressive therapies may prove more beneficial than stopping biologic therapy when patients do not respond during the first cycle. However it is challenging to initiate such therapies in the absence of a clearer evidence base and national/international guidelines to support their use. Our pragmatic approach has been to consider an individual patient's disease severity, their underlying co-morbidities, respecting individual patient preferences and, use of the clinically safest medications first. With this approach, if we then find that patients fail to respond clinically to high-dose anti-histamines and biologic therapies, we need to adopt individualised protocols

that are developed in partnership with patients/family/carers in order to achieve the best possible clinical outcome and minimise any medication related risks.

### List of abbreviations:

CSU	chronic spontaneous urticaria
UAS7	urticaria activity score over 7 days
TPO	thyroid peroxidase
TG	thyroglobulin
ANA	anti-nuclear antibody
ANCA	anti-neutrophil cytoplasmic antibody
dsDNA	double stranded DNA
G6PD	glucose-6-phosphate dehydrogenase level
IgE	immunoglobulin E
spIgE	specific IgE
anti-H1	anti-histamine
LTRA	leukotriene receptor antagonist
IgRT	immunoglobulin replacement therapy
s/c	subcutaneous
ANA	anti-nuclear antibody
SPEP	serum protein electrophoresis
GI	gastrointestinal
BW	body weight
IL-1	interleukin-1

### Ethics Approval and Consent to Participate

Formal ethical approval was not obtained as all investigations and treatments provided were dictated by clinical need and no research-based investigations or treatments provided to any of the patients. The authors certify that they have obtained all appropriate patient consent for clinical information to be reported. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

### Author contribution(s)

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## Availability of Data and Materials


All data related to particular cases are available with individual authors/clinicians that were in-charge of the patients, and further data (if relevant to the report) are available on request.

## Informed Consent

Formal ethical approval was not obtained as all investigations and treatments provided were dictated by clinical need and no research-based investigations or treatments provided to any of the patients. The authors certify that they have obtained all appropriate patient consent for clinical information to be reported. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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