

Rituximab in Refractory Chronic Spontaneous Urticaria: An Encouraging Therapeutic Approach

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Abstract

Background: Chronic spontaneous urticaria (CSU) is a frequent mast cell-driven disease that affects approximately 0.5–1% of the population. Antihistamines are currently the drugs of choice in patients with CSU. Omalizumab has been shown to be very effective in CSU and has been recently approved as second-line therapy. However, although its introduction has markedly improved the therapeutic possibilities for CSU, there is still a hard core of patients who do not respond and require effective treatment. **Methods:** We report the case of a patient who achieved an 8-month remission of refractory CSU following the use of rituximab, and perform a review of the literature regarding the use of rituximab in CSU. **Results:** There was a remarkable improvement in her CSU after the administration of rituximab maintained over time. **Conclusion:** Rituximab is a chimeric murine/human monoclonal antibody directed against CD20, which depletes memory B-lymphocytes that are necessary for autoantibody production. The abrogation of the autoantibody production is the proposed mechanism by which it may alleviate the symptoms of CSU.

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Chronic spontaneous urticaria (CSU) is a frequent mast cell-driven disease affecting 0.5–1% of the population. It impacts seriously on patients' quality of life [1], and antihistamines are currently the drugs of choice [2]. Omalizumab has recently been approved as a second-line therapy, but although its introduction has markedly improved the therapeutic possibilities for CSU, many patients do not respond. The mechanisms by which cutaneous mast cells are activated to induce hives in CSU are still not completely understood. However, it has been proposed that CSU might be due to autoimmune/autoreactive mechanisms. Based on these findings, some biologic agents have been proposed to control CSU with variable results [1, 3].

We report the case of a 44-year-old Caucasian female with a 9-year history of severe symptomatic CSU and an antisynthetase syndrome (ASS) anti-PL7 positive, with typical skin lesions and muscle biopsy of dermatomyositis and nonspecific interstitial pneumonia diagnosed in 2011. Five years after diagnosis, her CSU became unresponsive to H1-antihistamines at high doses (even up to fourfold), and could not even be controlled with the immunosuppressive drugs administered for her ASS: hydroxychloroquine, mycophenolate mofetil, azathioprine, intravenous immunoglobulins, tacrolimus, and oral prednisone (1 mg/kg/day). This led to severe impairment

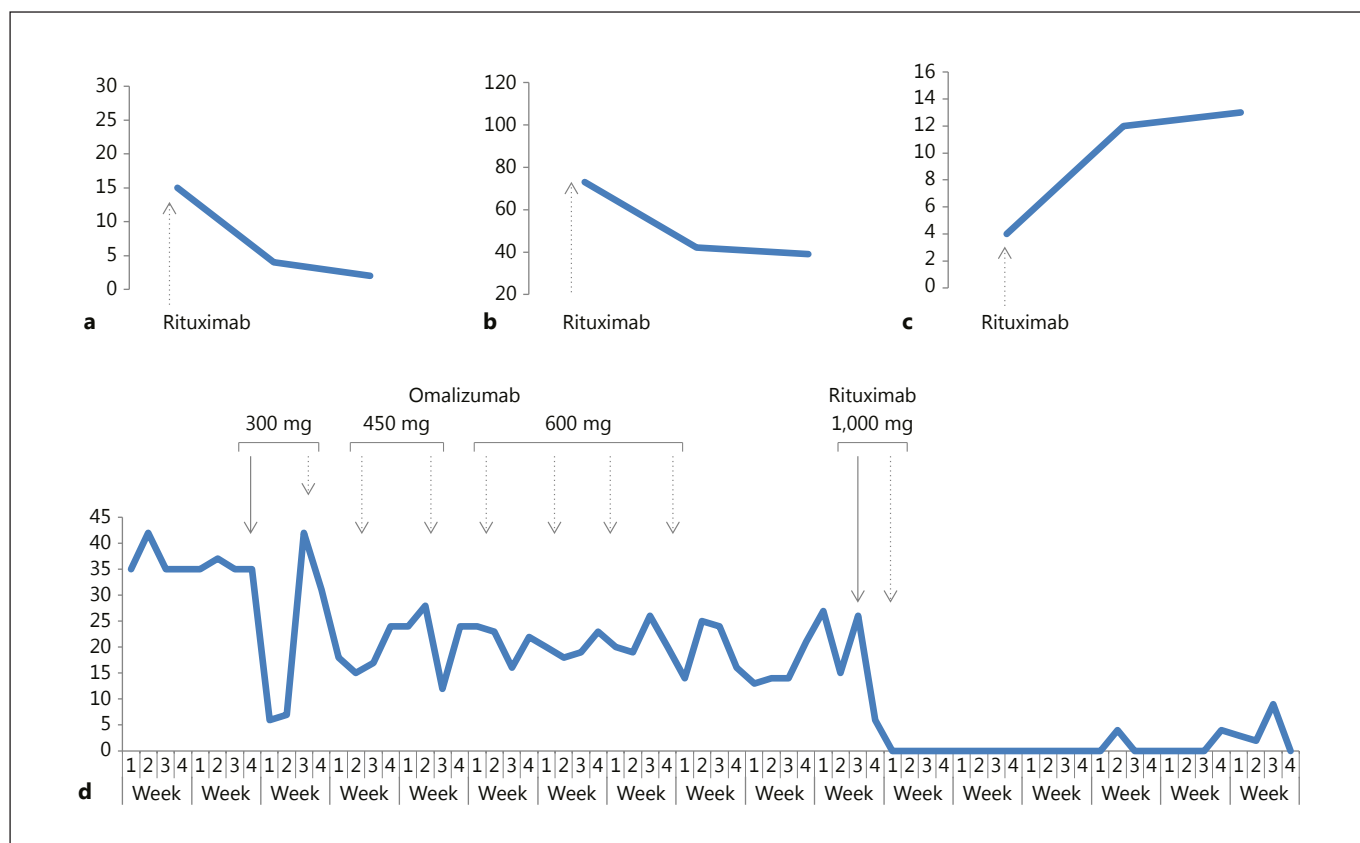


Fig. 1. Impairment of quality of life assessed by the Dermatology Life Quality Index (DLQI; **a**), the Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL; **b**), the Urticaria Control Test (UCT; **c**), and the Urticaria Activity Score 7 (UAS7; **d**). After the administration of omalizumab, a slight improvement of UAS7 was recorded; however, treatment was stopped after 8 months because a lack of response. DLQI, CU-Q2oL, UCT, and UAS7 improved strongly after the administration of rituximab.

of her quality of life as assessed by the Dermatology Life Quality Index (DLQI), the Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL), and the Urticaria Control Test (Fig. 1).

Screening for mutations in genes responsible for auto-inflammatory syndromes (MEFV, TNFRSF1A, MVK, NOD2, PAPA, NLRP3, PSTPIP1, CECR1, TMEM173) was negative, and a positron emission computed tomography showed no abnormal findings. Skin biopsy was consistent with CSU, and a prick test showed no abnormal reaction.

Accordingly, omalizumab (300 mg subcutaneous every 4 weeks) was started. Drug dosage was increased due to lack of response (450 mg at the 3rd month and 600 mg at the 5th month), and was finally discontinued after the 8th monthly dose. Montelukast (10 mg/d) also failed to control the symptoms.

Because of a relapse of her ASS, treatment with rituximab, 2 doses of 1,000 mg intravenously with a 2-week interval, was administered. Rituximab showed rapid effectiveness, with complete relief of symptoms and normalization of CPK and LDH within 1 week of the administration of the first dose. Concomitantly, hives and pruritus disappeared completely within 72–96 h of the administration of the first dose. There were no adverse events while and after rituximab administration. The remarkable improvement in her CSU after the administration of rituximab is shown in Figure 1. The response to rituximab was maintained for 8 months with infrequent mild flares of CSU that have been easily managed with low-dose antihistamines.

Rituximab is a chimeric murine/human monoclonal antibody directed against CD20, which depletes memory B-lymphocytes that are necessary for autoantibody pro-

Fig. 2. Omalizumab binding only to IgE, and rituximab binding to both FcεR1α and IgE. Functional IgG autoantibodies against FcεR1α, and less commonly against IgE, have been reported in patients with CSU, which are thought to directly contribute to the pathophysiology of the disease through the activation of basophils and mast cells.

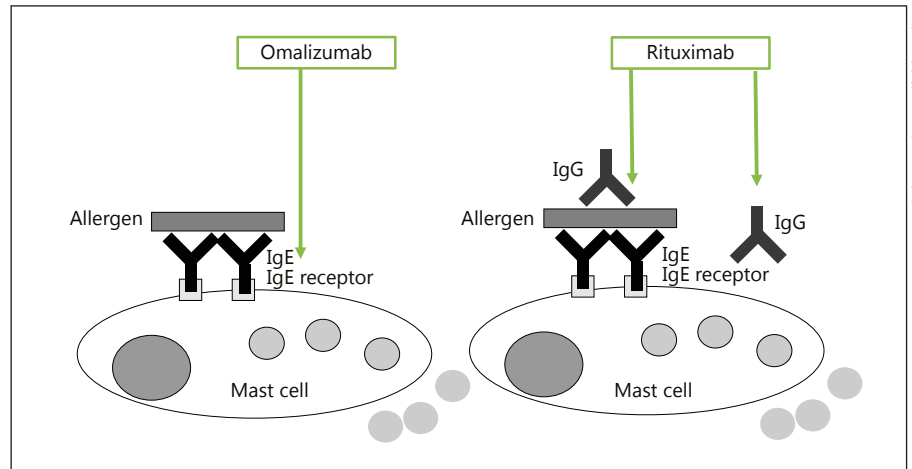


Table 1. Five case reports regarding use of rituximab in patients with CSU have been reported

Title	First author [Ref.]	Year	Patients, <i>n</i>	Sex	Age, years	Previous treatments	Rituximab dose	Response to rituximab	Delay	Sustained response
Remission of refractory chronic spontaneous urticaria following the use of rituximab	Combalia	2017	1	Female	44	Antihistamines, mycophenolate mofetil, azathioprine, intravenous immunoglobulins (IVIG), tacrolimus, prednisone, omalizumab, montelukast	2 doses of rituximab 1,000 mg with a 2-week interval	Yes	<1 week	8 months
Rituximab for the treatment of recalcitrant chronic autoimmune urticaria	Steinweg [6]	2015	1	Female	38	Antihistamines, prednisone,	2 doses of rituximab 1,000 mg with a 2-week interval	Yes	2 weeks	10 months
Rituximab successfully treats refractory chronic autoimmune urticaria caused by IgE receptor autoantibodies	Chakravarty [7]	2011	1	Female	51	Antihistamines, prednisone, cyclosporine, mycophenolate mofetil	4 weekly infusions of rituximab 375 mg/m ² + metotrexate 15 mg/week	Yes	6 weeks	8 months
Anti-CD20 or anti-IgE therapy for severe chronic autoimmune urticaria	Arkwright [8]	2009	1	Male	12	Antihistamines, prednisolone	4 weekly infusions of rituximab 375 mg/m ²	Yes	1 week	12 months
Lack of response of severe steroid-dependent chronic urticaria to rituximab	Mallipeddi [9]	2007	1	Male	33	Antihistamines, prednisone, IVIG, cyclosporin, dapsone, sulfasalazine, azathioprine, doxepine, amitriptyline, colchicine, hydroxicloroquine, danazol, NBUVB phototherapy	4 weekly infusions of rituximab 375 mg/m ²	No	–	–

In 4 patients (80%), a successful outcome of CSU was demonstrated after the administration of rituximab. In all of the patients, the effect of rituximab was seen shortly after the administration (1–6 weeks) and was maintained during >8 months.

duction. This abrogation is the proposed mechanism by which symptoms of CSU may be alleviated [1, 3]. Functional IgG autoantibodies against FcεR1α, and less commonly against IgE have been reported in patients with CSU [4]. They are thought to directly contribute to the pathophysiology of the disease through the activation of basophils and mast cells, and subsequent histamine release. It would then, be reasonable to devise a more targeted approach to treating nondirect IgE-mediated forms of CSU (Fig. 2). Moreover, taking into consideration that rituximab has also been used in lymphocyte T-mediated diseases such as rheumatoid arthritis or systemic lupus erythematosus, it might also be effective through this pathway.

Rituximab is a safe and well-tolerated drug, although some patients might experience mild to moderate infusion-related reactions during its administration, which decrease substantially with subsequent infusions. Due to B-lymphocyte depletion, localized fungal and herpes virus infections are commonly reported; however, as T cells are unaffected, opportunistic infections rarely occur as a secondary effect. Hematological abnormalities (mostly

neutropenia) have been reported in a minority of patients, and are usually mild and reversible [5].

Only 4 other cases regarding the use of rituximab in patients with CSU have been described (Table 1). The data are encouraging; there are, however, still no randomized blinded trials. Further studies should be performed to determine the role of rituximab and other B-cell therapeutics in patients with severe CSU.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflict of interest to declare.

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