Case Report

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2022.42.006698

Rituximab in Treatment of Chronic Spontaneous Urticaria

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ARTICLE INFO

Accepted: February 07, 2022

Published: February 22, 2022

Citation: Saira Zafar, Erin McGintee, Alan Wolff1, Arthur Torre, Steven E Schutzer. Rituximab in Treatment of Chronic Spontaneous Urticaria. Biomed J Sci & Tech Res 42(1)-2022. BJSTR. MS.ID.006698.

Abbreviations: CSU: Chronic Spontaneous Urticaria; IVIG: Intravenous Immunoglobulin; PML: Progressive Multifocal Leukoencephalopathy; CVID: Common Variable Immune Deficiency

ANNOTATION

Background: Chronic spontaneous urticaria (CSU) is defined by urticaria and/or angioedema for at least 6 weeks. It is usually treated with antihistamines, omalizumab, or other immunosuppressive therapy; however, these treatments often do not work.

Objective/Methods: The following case series describes 8 of 9 patients with CSU successfully treated with rituximab.

Results: Our first patient was unresponsive to antihistamines, immunosuppressive therapy, and omalizumab and obtained complete resolution with rituximab. Another patient failed natalizumab treatment of her multiple sclerosis and started rituximab, which incidentally resolved her CSU. Our third patient refractory to antihistamines, dapsone, cyclosporine, omalizumab, and steroids obtained complete resolution after starting rituximab. The use of rituximab in CSU has been reported in five patients according to our review of the literature; of these, four responded. The patient who did not respond had both pressure urticaria and CSU. The next patient was a boy unresponsive to antihistamines; rituximab was started and his CSU then resolved. The third patient was a woman who was able to discontinue corticosteroids after initiation of rituximab. The next patient was refractory to antihistamines, mycophenolate mofetil, cyclosporine, and corticosteroids and had complete resolution of symptoms after starting rituximab. The fifth patient failed antihistamines and steroids and was hospitalized with angioedema; she was treated with rituximab and was symptom free after her second infusion.

Conclusion: A clinical trial to study the safety of rituximab in chronic urticaria showed promising results however the was terminated prematurely by the FDA because of case reports of rituximab-induced PML. Since then, studies have revealed that rituximab-induced PML is rare. In summary, eight of nine patients with recalcitrant urticaria successfully responded to rituximab after failing many therapeutic agents. The use of rituximab in treatment of CSU should be considered for cases of urticaria resistant to conventional treatment.

Introduction

Chronic spontaneous urticaria (CSU) is a condition defined by the presence of urticaria, angioedema, or both, on most days of the week for a minimum of 6 weeks duration. There are several postulated theories as to the etiologies of CSU that are frequently disputed with the exception of the autoimmune subtype of CSU, which is widely accepted. Two autoantibodies have been identified, one to the high-affinity IgE receptor FcεRI, and the other to the Fc portion of IgE. These two autoantibodies are found in approximately

30-50% of patients with CSU [1]. Conventional treatment of CSU typically involves second generation H1-antihistamines followed by the use of omalizumab for antihistamine-refractory cases. Current literature reports a response rate of 38.6% with standard antihistamine dosing; of the unresponsive patients, an additional 63.2% of patients may obtain control with higher doses (up to four times the conventional dose) of second generation H1-antihistamines [2]. Furthermore, many patients do not achieve resolution of symptoms despite trialing multiple therapies including antihistamines, doxepin, leukotriene receptor antagonists, omalizumab, and immunosuppressive therapy with corticosteroids, dapsone, hydroxychloroquine, methotrexate, mycophenolate mofetil, cyclosporine, azathioprine, and/or intravenous immunoglobulin (IVIG) [3]. This leads to a significant decrease in quality of life with higher incidences of anxiety and depression [4]. The following case series describes our 3 patients and 5 additional case reports of chronic spontaneous urticaria refractory to the prior mentioned therapies, with 7 of the 8 patients successfully treated with rituximab.

Cases

Our first patient is a 43 year-old woman with psoriatic arthritis and autoimmune thyroiditis who presented to us with chronic spontaneous urticaria. She was found to have elevated levels of anti-IgE receptor antibodies with levels greater than maximum level of detection. She was unresponsive to high doses of antihistamines, cyclosporine, prednisone, dapsone, mycophenolate mofetil, hydroxychloroquine, and omalizumab and ultimately trialed on rituximab with complete resolution of urticaria. She continued rituximab (2000mg every 6 months) with sustained response. Our second patient is a 49 year-old woman with multiple sclerosis, allergic rhinitis, and atopic dermatitis who was referred with humoral immunodeficiency. She was diagnosed with common variable immune deficiency (CVID) and started on subcutaneous immune globulin therapy. She also had long-standing generalized urticaria refractory to antihistamines and subcutaneous immune globulin. Natalizumab was initially trialed for treatment of her multiple sclerosis, however she failed therapy and was subsequently started rituximab, which incidentally resolved her urticaria. Our third patient is a 48 year-old woman with hypertension and asthma who presented to us with complaints of long-standing urticaria refractory to antihistamines, dapsone, cyclosporine, omalizumab, and high doses of steroids (prednisone 20mg BID).

She was started on rituximab with complete resolution of urticaria following the second infusion. The novel use of rituximab in treatment of CSU has been reported in a total of five patients according to our review of the literature. Of the five patients, four responded with resolution of symptoms, and one did not experience any response. The patient who did not respond was a 33 year old man with both urticaria and angioedema with pressure-induced urticaria of the hands and feet [5]. His urticaria first began when he was a prisoner in a Taliban jail in Afghanistan. He was treated with oral corticosteroids (10-60mg daily) to maintain acceptable control for a total of three years. Basophil histamine-release assay was positive, indicating likely autoimmune urticaria. Other attempted treatments included IVIG, cyclosporine, dapsone, montelukast, sulfasalazine, azathioprine, doxepin, amitriptyline, fluoxetine, colchicine, hydroxychloroquine, danazol, and narrow-band UVB phototherapy. He was then trialed on rituximab, however was not noted to have any change in symptom scoring or steroid requirement at the 6 month mark. The next patient treated with rituximab was a 12 year-old boy with humoral immunodeficiency (Smith-Magenis Syndrome) and type 1 diabetes mellitus on IVIG with chronic urticaria and angioedema who was only partially responsive to oral antihistamines [6]. Initially, his urticaria improved with initiation of IVIG and he was able to discontinue antihistamines completely, however 2 years later he developed severe chronic urticaria and angioedema that was completely refractory to antihistamines.

Oral prednisolone (20-30mg/day) was initiated, however he experienced decreased glycemic control. The decision was then made to trial rituximab and within 1 week of his first dose his urticaria and angioedema resolved. He was able to discontinue all antihistamines and prednisolone, and remained symptom free for 12 months, after which time his urticaria returned, this time controlled with desloratadine. The third patient was a 19 year-old woman with recurrent facial angioedema. Initially, symptoms were controlled with oral antihistamines, however subsequent episodes became more severe with airway compromise and more aggressive management required in the emergency room [7]. Oral ranitidine was added to her regimen of 10mg cetirizine twice daily, however she continued to experience severe episodes, one requiring very high doses of epinephrine and a 48-hour admission for intravenous corticosteroid treatment, which when transitioned to high dose oral steroids, failed and resulted in recurrent angioedema requiring rehospitalization. C1 esterase inhibitor level and function was noted to be normal. She was then started on hydroxychloroquine as well as IVIG, and both were discontinued due to a generalized seizure with posterior reversible encephalopathy syndrome following her second dose of IVIG. She was then trialed on dapsone which was discontinued due to methemoglobinemia and hemolytic anemia.

She finally underwent tracheostomy due to complications from prolonged high-dose corticosteroid therapy. Rituximab was then considered, and she was started on intravenous treatment for 4 weeks. By the fourth infusion, she was able to be weaned off oral corticosteroids without recurrence and her tracheostomy was

reversed. The next patient was a 51 year-old woman who presented with a 1-year history of urticaria associated with abdominal pain, vomiting, and diarrhea [8]; C1q, C1 esterase, CH50 levels, and tryptase levels were all within normal limits. A bone marrow biopsy was negative for mastocytosis. She also had positron emission tomographic-computed tomographic scan, repeat endoscopies, and colonoscopies; all of which were unrevealing for any abnormalities. Her IgG autoantibody against FcεRIα on immunohistochemistry was noted to be positive (CD203c expression 8.1% (normal range, 0.0% to 5.0%)). She failed treatment with oral antihistamines and both oral and intravenous corticosteroids; mycophenolate mofetil was trialed and discontinued due to gastrointestinal symptom flare. Cyclosporine was initially helpful in controlling her symptoms for one year before she developed breakthrough urticaria, vomiting, and diarrhea. Four weekly infusions of rituximab were then administered, and the patient was noted to have complete resolution of symptoms at the 6-week mark.

The fifth patient reported in the literature was a 38 year-old woman who presented with a one-year history of urticaria and facial angioedema. She was trialed on maximal therapies of antihistamines without relief and was then started on 60mg prednisone daily [9]. She was hospitalized soon afterwards with an acute flare of urticaria, despite being on 60mg prednisone daily, and was treated with 1 gram rituximab infusion overnight. She was discharged the next day with improved control of urticaria, and was given a second infusion two weeks later, after which she remained symptom free for the following 10 months.

Discussion

CSU affects approximately 1% of the general US population at some point in their lifetime, typically in the third to fifth decades of life [5,10]. Current guidelines recommend treatment with H1-antihistamines up to four times the conventional dose and up to 40% of patients will respond to this therapy. In patients without control of symptoms with H1-antihistamines, omalizumab and/or cyclosporine are typically trialed next [2]. Omalizumab is a recombinant humanized anti-IgE monoclonal antibody approved for treatment of antihistamine-resistant CSU in patients 12 years of age and older and it is the only non-antihistamine drug licensed for use in treatment of CSU [5]. The monoclonal antibody downregulates FcεRI expression on mast cells and basophils by binding the C3 domain of the IgE heavy chain [11], therefore preventing degranulation and urticaria. Approximately 70% of patients with CSU obtain control of symptoms with omalizumab infusion alone, and up to 80% of patients obtain symptom control with maximal doses of antihistamines in addition to omalizumab infusions [12]. Rituximab is a chimeric murine/human anti-CD20 monoclonal antibody approved for use in many autoimmune and hematologic disorders, however it's use in treatment of chronic spontaneous urticaria remains limited to isolated case reports. It targets CD20 which is present in high levels on B cells.

Following antibody binding, B cells die by a number of mechanisms including antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, and apoptosis By targeting these cells that in turn produce IgE & IgG autoantibodies against FcεRI, it is postulated that better control of chronic urticaria may be obtained [12]. An interventional clinical trial was initiated in 2006 to study the safety of rituximab in chronic urticaria (The Rituximab Urticaria Study- "RUSTY"). Fifteen patients were enrolled in a non-randomized, open-label, single group assignment, and results were promising, however the trial was terminated prematurely by the FDA because there were case reports of rituximab induced progressive multifocal leukoencephalopathy (PML) in rheumatic diseases. Since then, studies have revealed that the incidence of rituximab-induced PML is exceedingly rare, with rates of 2.56 per 100,000 patients with rheumatoid arthritis and <1 per 10,000 patients with granulomatosis with polyangiitis and microscopic polyangiitis [13]. It also revealed that all confirmed PML cases were associated with other risk factors independent of rituximab treatment. Although the risk remains low for the prior mentioned patient populations, it has previously been suggested that autoimmune diseases can predispose patients to the development of PML 14, which is an important consideration for the chronic autoimmune urticaria population.

In summary, we report seven of eight patients with recalcitrant urticaria who successfully responded to treatment with rituximab after failing many second and third line therapeutic agents. It is believed that rituximab works by removing B-lymphocytes from the circulation, resulting in lowered levels of autoantibodies directed at either IgE or it receptor, but exactly how it works is incompletely elucidated. Further research is required to determine the impact of chronic autoimmune urticaria on the development of PML, however the use of rituximab in treatment of CSU should be entertained as possible therapy for cases of treatment-resistant chronic urticaria, especially when encountered in the setting of other autoimmune conditions.

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