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Case Report

Role of Rituximab in Keratoconjunctivitis Sicca due to Sjogren Syndrome

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Abstract

Introduction: In the ophthalmologic field is not uncommon to find signs and symptoms derived from systemic pathologies. Such cases demand a comprehensive approach that allows full control of the ophthalmic manifestations that can be as severe as ulceration or ocular perforation.

Case presentation: We describe three cases of Sjogren's syndrome based on ocular and oral symptoms as well as salivary gland biopsy and presence of auto-antibodies, who received conventional topical treatment and systemic immunosuppression and were expected to improve his symptoms and prevent progression of the disease. However, after identifying the failure of this treatment, we decided to switch to biologic therapy with rituximab.

Conclusions: After therapy with steroids or immunosuppressants has failed, treatment with rituximab should be considered. Improvement in objective variables like Schirmer's test and ocular surface stain as well as subjective component of symptoms and comfort can be achieved.

INTRODUCTION

In the ophthalmologic field is not uncommon to find signs and symptoms derived from systemic pathologies, usually autoimmune diseases; such cases demand a comprehensive approach that allows full control of the underlying disease in order to achieve symptom relief of the ophthalmic manifestations that can be as severe as ulceration or ocular perforation.

Rituximab has become a very effective option to control ophthalmic symptoms secondary to systemic diseases especially when the patient is accurately selected as candidate for the treatment according to the possible side effects requiring close follow up by ophthalmologist and rheumatologist.

In this article we describe the case of three patients with diagnosis of Sjogren's syndrome based on ocular and oral symptoms as well as salivary gland biopsy and presence of auto-antibodies, who received conventional topical treatment and systemic immunosuppression and were expected to improve his symptoms and prevent progression of the disease; however, after identifying the failure of this treatment, we decided to switch to biologic therapy with rituximab, and the response will be described later here.

Rituximab is a genetically modified monoclonal antibody, derived from mammal cell cultures to obtain a kappa immunoglobulin of IgG_1 with two heavy chains containing 451 amino acids and two light chains with 213 amino acids each one [1].

It shows high affinity for the CD_{20} antigen, trans-membrane protein, found on the surface of B lymphocytes. This antigen acts as a calcium channel allowing activation of the lymphocyte and inducing progression and differentiation of the cell cycle [2]. The final outcome of the medication is to reduce the pool of B lymphocytes by induction of antibody mediated cytotoxicity; complement mediated cellular lysis, blockade of cell cycle and apoptosis. The side effects associated to its use are related to the release of cytokines, specifically Tumor Necrosis Factor alpha (TNF) and Interleukin 6 (IL) [3].

It has been observed sensitization of B cells on certain chemotherapy resistant lymphomas, associated with the use of the drug, inducing apoptosis on malignant cells. The use of Rituximab on systemic diseases relies on the low affinity for non-lymphoid tissue.

After the third dose, reduction of all B cells can be observed, circulating and in tissue, keeping the levels low for as long as 6 to 9 months after finished treatment; the levels can become normal after 12 months. Resistance can be achieved with the under expression of CD_{20} on the surface of B cells associated with lymphopenia and normal immunoglobulin levels.

Rituximab is approved by the FDA for the use in rheumatoid arthritis, chronic lymphocytic leukemia, Non-Hodgkin lymphoma, Granulomatosis with Polyangiitis (formerly Wegener's granulomatosis), Microscopic Polyangiitis and others. There are elements regarding the mechanism of action that are still under research [4].

CASE PRESENTATION

We present 3 cases of patients successfully treated with rituximab for Sjogren's syndrome (SS).

Case 1

A 29-year-old man with a 3-year history of severe SS secondary to rheumatoid arthritis was referred to our department for treatment. He was previously treated with preservative-free lubricants, topical cyclosporine and bilateral punctal plugs. His best- corrected visual acuity (BCVA) at presentation was OD 20/100 and OS 20/200, Schirmer test with anesthesia, 0 mm; tear film breakup time with fluorescein, 1 second; fluorescein test using the Oxford grading scheme was graded V (severe). Superficial punctate keratopathy, filamentary keratitis, and epithelial edema were observed as well. Treatment with lubricants, autologous serum drops, and topic cyclosporine was initiated. During the follow-up, systemic pilocarpine was prescribed as well. No improvement was observed after 6 months on maximal tolerated therapy. Later on, conventional immunosuppressive pharmacotherapy was initiated due to previous poor response. A decision was made in collaboration with the department of rheumatology to initiate rituximab with a dose of 375 mg/m^2 in May 2005. A weekly intravenous infusion was administered for 4 weeks; mild dizziness ensued after the first injection. Subsequently, the patient complained of dry cough for a week after the third dose. One month after the last injection, in July 2005, Schirmer test with anesthesia was OD 1 mm and OS 3 mm. The breakup time with fluorescein was 4 seconds. Fluorescein test was graded III (moderate). The keratitis improved; therefore, a reliable refraction could be performed, BCVA was found to improve to OD 20/50 and OS 20/30. Systemic symptoms had also subsided, and the patient was able to return to work. After 6 months of an uneventful course, his condition relapsed and as a result BCVA dropped to OD 20/150 and OS 20/80. Fluorescein test graded V (severe). Severe keratitis, filamentary keratitis, and associated epithelial edema were observed as well. Therefore, the patient underwent a fifth cycle of rituximab without complications in May 2006. The KCS (kerato-conjunctivitis sicca) related symptoms were minimal at the first month follow-up visit. A significant BCVA improvement was recorded with OD 20/60 and OS 20/40. Schirmer test with anesthesia was 2mm OD and 1mm OS. Fluorescein test was graded III (moderate). Superficial punctate keratopathy had improved, and neither filamentary keratitis nor corneal ulcers were observed. Topical cyclosporine and autologous serum drops were successfully discontinued. This patient's condition was subsequently controlled with only lubricants and systemic pilocarpine without a relapse for 6 months when the last evaluation was performed.

Case 2

A 39-year-old woman with a history of red eye and pruritus came for consultation in May 2003. She also complained of poor salivation and fatigability. Superficial punctate keratopathy was observed in the inferior cornea. Schirmer test with anesthesia was 4 mm in both eyes. Tear film breakup time with fluorescein was 3 seconds. A diagnosis of KCS was made. Therapy including preservative-free and viscous lubricants was prescribed. The patient was also referred for an assessment by a rheumatologist. Primary SS was diagnosed by biopsy and by serum antibodies. In the following evaluation, in May 2004, systemic pilocarpine, omega-3 fatty acids and bilateral punctal plugs were initiated without symptom improvement. In the following months, different lubricants, autologous serum drops and topical cyclosporine were tried; however, poor tolerance to the treatment was observed. In May 2005, she worsens with severe KCS and thus could not use the computer, resulting in employment complaints. Schirmer test with anesthesia was 3 mm in both eyes. Breakup time was 3 seconds. Fluorescein test was graded IV (marked). In July 2005, a weekly intravenous infusion of rituximab was started (375 mg/m^2) along with methylprednisolone 500 mg weekly for 4 weeks. With the infusion, the patient experienced dyspnea, weakness, and depression. Improvement in the KCS-related symptoms was observed, as well as no evidence of keratitis after 1 month of treatment. Fluorescein test was graded I (minimal). Schirmer test with anesthesia remained OD 15 mm and OS 9 mm throughout the following 8 months. KCS eventually relapsed in May 2006, leading to worsening in this patient's symptoms and keratitis. Schirmer test was 3 mm. Breakup time was 3 seconds. Fluorescein test was graded IV (marked). The patient declined a new cycle of rituximab because she was concerned about her previous infusion-related discomfort.

Case 3

A 45 year old female with diagnosis of severe SS associated with ocular and systemic involvement very resistant to treatment, is initially treated with multiple eye drops for her dry eye symptoms but with poor improvement. Cyclosporine is added and subdermal injection of steroids in the eyelids is performed; she doesn't complain of poor vision but remains symptomatic with severe pain that interferes with her daily activities. It was decided to administer a pulse of methylprednisolone and conventional treatment for immunosuppression on the search for improvement of symptoms; however, the persistence of those forced us to contact the rheumatology department for a better therapeutic option for this patient.

After 2 years of symptom onset, the first dose of the rituximab was administered; the patient showed notorious improvement of her ocular complaints but several side effects were also observed, the most significant was severe headache with signs of increased intracranial pressure which required strict follow up during drug administration; slowly, the patient showed improvement and no more side effects were found. One month after the medication was stopped, the ocular symptoms relapsed for which rituximab was reinitiated. Currently, the patient has been getting one dose of Rituximab every 6 months, on her fourth dose so far, no signs of side effects have been detected and her symptoms have subside; full compliance and satisfaction with the treatment are reflected on improvement of her quality of life.

DISCUSSION

Primary Sjogren's syndrome is an autoimmune systemic disease characterized by infiltration of the exocrine glands by focal aggregates of lymphocytes grouped together surrounding ducts; the symptoms associated are dry eye, dry mouth and chronic swelling of salivary glands [5]. Extra-glandular symptoms

observed are chronic fatigue, arthritis, pulmonary edema, vasculitis, neuropathy, renal tubular acidosis and hematologic abnormalities.

Exocrine glands involvement includes monocytic periductal infiltrate, B and T CD4 lymphocytes, due to presence of autoantibodies anti SS-A/Ro and anti SS-B/La, rheumatoid factor, hypergammaglobulinemia and 44-fold risk of developing B cell lymphoma, specifically mucosal-associated lymphoid tissue (MALT) lymphoma [6,7]. The binding of rituximab to CD_{20} expressing cells leads to a significant depletion of immune cells by antibody dependent cellular toxicity and apoptosis. The role of the hyperactivity of the B cells in the pathogenesis of SS is the major support for the use of rituximab.

Schirmer's test has been used to measure tear production in most of the published studies, but its reliability is low and not very sensitive in detecting minimal changes in time [8]. Only one study done by Carubbi and collegues was able to prove increase in Schirmer's test in patients treated with rituximab vs control [9]. Ocular surface integrity assessed with Rose Bengal or Lissamine green stain, is more reliable and accurate for the evaluation of Keratoconjunctivitis sicca in SS [10]; studies using this method were able to demonstrate improvement in parameters after treatment, attributed to the effect of rituximab on the morphology and function of the lacrimal gland, composition of the tear film and effect on the inflammatory component of the ocular surface disease [11,12].

Subjective variables are measured with the visual analog scale (VAS), there are four different scales used in SS: global disease, fatigue, pain and dryness; most of studies have shown positive outcomes with lower scores in the VAS of ocular and oral dryness [13].

The TEARS [14] (Tolerance and Efficacy of Rituximab in Primary Sjogren's Syndrome) trial published in 2014 included 120 patients from 12 university hospitals, with a score higher than 50-mm in at least 2 out of 4 VAS and recent onset of disease (less than 10 years); 63 were treated with rituximab plus methylprednisolone and 57 with placebo plus methylprednisolone. The primary outcome was an improvement equal or better than 30-mm in at least 2 of the 4 VAS by the 24^{th} week compared to the initial measure. There wasn't statistically significant difference in between both groups for the primary outcome, but there was higher improvement of the dryness VAS in the rituximab group compared to the control group.

Later on, in 2015 a post-hoc analysis was published. The Sjogren's syndrome responder index (SSRI), was thought to asses more accurately the response to treatment in patients with Sjogren's syndrome; it combined the VAS for fatigue, oral and ocular dryness with the unstimulated whole saliva (UWS) and the erythrocyte sedimentation rate (ESR). It was found that if the TEARS trial's results were analyzed with this new tool, the proportion of patients with 30% improvement measured by SSRI in the rituximab group are much higher than in the control group, with statistic difference [15].

Quality of life between SS´s patients is severely affected to the point of being comparable with rheumatoid arthritis and fibromyalgia patients [16]; some studies have found a negative impact of dry eye over quality of life, similar to patients with moderate to severe angina [17]. According to this, there's good evidence to support the use of advanced therapies in SS even in the absence of systemic findings.

Vivino and collegues in 2016 published an update on the treatment guidelines for SS; they acknowledge Rituximab as the only biologic treatment with sufficient evidence to be indicated for dry manifestations of SS when first line treatment fails, and also for the treatment of systemic findings related to SS such as cryoglobulinemia, vasculitis, inflammatory arthritis, pulmonary symptoms and peripheral neuropathy [18].

Precaution is advised by the time of infusion due to risk of side effects like hypersensitivity type reactions, tumor lysis syndrome in patients with non-Hodgkin lymphoma, progressive multifocal leukoencephalopathy, reactivation of hepatitis B with risk of fulminant hepatitis, severe mucocutaneous reactions; bacterial, viral or fungal severe infections, intestinal obstruction and perforation, cardiac arrhythmias and angina. Avoid live inactivated vaccines during treatment.

CONCLUSION

Keratoconjunctivitis sicca secondary to SS presents in different severity grades requiring stepwise treatment starting with topical to systemic medication to achieve adequate control of inflammation and improve tear production.

After therapy with steroids or immuno suppressants has failed, treatment with rituximab should be considered. Improvement in objective variables like Schirmer's test and ocular surface stain as well as subjective component of symptoms and comfort can be achieved, but precaution with infusion and close follow up must be considered.

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