A patient with refractory oral pemphigus vulgaris successfully treated with a biologic drug- Rituximab: A case report.

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ABSTRACT:
Pemphigus vulgaris (PV) is a chronic autoimmune blistering disease affecting mucous membranes and the skin. Rituximab (RTX), a monoclonal antibody against CD20, has been approved by FDA for the treatment of adults with moderate to severe PV. A 42-year-old Indian woman, with refractory oral PV presented to our clinic with painful erosions and ulcers of her oral mucosa. She was treated with available evidence based immunosuppressants with limited success over a period of 8 years. RTX was given observing the lymphoma protocol. Her symptoms improved dramatically after the first month of RTX with sustained resolution on low doses of prednisone, mycophenolate mofetil and no significant new lesions appearing to date. Her quality of life improved significantly. RTX seemed an effective treatment for refractory oral PV.

Keywords: Pemphigus vulgaris, rituximab, autoimmune, mucocutaneous.

INTRODUCTION: Pemphigus vulgaris (PV) is a chronic autoimmune blistering disease affecting mucous membranes and the skin in which specific antibodies directed against desmoglein Dsg3 and Dsg1 are detected. These are transmembrane proteins found on the cell-cell junctions of keratinocytes (called as desmosomes) that maintain the tissue and cell integrity. If the autoantibodies are against Dsg3, the disease manifests as oral lesions. The auto-antibodies against Dsg1 presents with cutaneous lesions. However, it is not uncommon to have patients presenting with oral lesions and then progressing with generalized skin lesions. The standard first-line and evidence based treatment of PV are systemic corticosteroids with adjuvant immunosuppressive agents (azathioprine, mycophenolate mofetil). However, some cases are refractory to the latter treatments or suffer from side effects of the drugs or are not eligible due to other co-morbid systemic diseases (i.e. diabetes)1. Rituximab (RTX) is a chimeric human-mouse monoclonal antibody against the transmembrane antigen CD20 which is expressed on B lymphocytes1. After the binding of RTX to CD20, normal and pathogenic B-cells are depleted; whereas terminally differentiated plasma cells are spared1. RTX is approved for the treatment of CD20+ B-cell non-Hodgkin lymphoma, CD20+ chronic lymphocytic leukemia and Rheumatoid arthritis (RA) unresponsive to TNFα antagonists. RTX has been reported to be used off-label for autoimmune diseases as well following its successful use for paraneoplastic pemphigus associated with B-cell non-Hodgkin lymphoma2. RTX has recently been approved by the FDA (2018, USA) for the treatment of adults with moderate to severe PV3. According to the European guideline, RTX is indicated for patients who remain dependent on more than 10 mg prednisolone combined with an immunosuppressive adjuvant4. The International Bullous Disease Consensus Group has also recently recommended the use of RTX and corticosteroids as first line therapy options for moderate to severe PV5. We document the first case of refractory oral PV in South Africa that was successfully treated with RTX.

CASE:
In 2012, a 42-year-old Indian woman presented to the Charlotte Maxeke Johannesburg Academic Hospital in Johannesburg, Gauteng Outpatient Clinic with painful ulcers affecting her oral mucosa of six-month duration. She had no systemic diseases (diabetes, thyroid disease) and was not on any systemic medication. She was diagnosed with oral PV at the Nelson Mandela Medical School UKZN, Natal in 2006, confirmed on tissue histology and
immunofluorescence findings. Intralesional steroids, monthly intravenous pulses of methylprednisolone, IV and oral cyclophosphamide and intravenous immunoglobulin (IVIG) induced lessening of her oral symptoms but sustained improvement or remission was never achieved. She was maintained on combination systemic therapy of low dose prednisone, mycophenolate mofetil (MMF) with tetracycline and nicotinamide on a continuous basis. She moved provinces and presented to us with deep painful erosions and ulcers on her tongue, buccal mucosae and soft and hard palate. She had no skin, scalp, nail and dental changes. Her blood pressure was 120/80 mmHg and physical examination was all normal. Her disease affected her speech, diet and her personal quality of life. Her mucosal lesions were consistent with a diagnosis of oral PV, and we obtained the histopathology and immunohistochemistry report from the previous institution. The biopsies were not repeated. Endoscopy at the Gastroenterology Unit revealed oesophageal erosions and cricopharyngeal ulcerations. We continued her previous treatment, and added cyclosporine (100 mg bd) both systemically and as mouth washes intermittently, and maintained her on high doses of both MMF (2g/daily) and systemic steroids (10 mg/daily). Despite these evidence based therapeutic interventions; she did not achieve a clinical state of remission. She lived on liquidized food and had a poor social life. She stopped working because of the morbidity of oral PV and her personal life suffered. In November 2016 with a diagnosis of refractory oral mucosa dominant PV, we obtained permission from her insurer to use RTX. RTX was given at 375 mg/m² body surface area weekly over 4 consecutive weeks in combination with prednisolone (20 mg/day) and MMF (2 g/day) using the lymphoma protocol. She complained of mild flu like symptoms during the infusion which resolved spontaneously. She had no serious adverse events during or after the treatment. Her blood count, erythrocyte sedimentation rate (ESR) and monitoring of her liver and kidney functions were normal. Her oral lesions improved dramatically after the first month of RTX with no significant new blisters, ulcers or erosions appearing to date (Figures 1 and 2). The CD19+B lymphocyte counts 1 month and 1 year after the RTX treatment was zero and 272 cell/uL (78-899 cell/uL) respectively. Unfortunately anti-Dsg antibody levels were not done prior to this treatment. During the 20-month follow-up period, she remained in remission without any need for a second course of RTX. She is being maintained on lower systemic prednisolone (5mg/day) and MMF(500mg/day). She now eats solid foods and enjoys a normal social life.

Figure 1: Oral ulcerations located on her tongue, both buccal mucosae and the soft and hard palate
DISCUSSION:
PV is a lifelong autoimmune blistering disorder which needs complex interventions directing multiple pathogenic pathways. Oral mucosal ulcerations are frequently the site of initial presentation of PV. Due to the chronic and recalcitrant nature of the disease, our patient had to be treated with multiple immunosuppressive drug combinations with little effect on disease control, and RTX was the only eventual treatment that induced a state of remission. Since the optimal dosing regimen of RTX in autoimmune blistering diseases is not known, it has been used either with rheumatoid arthritis protocol (2x1000mg-2 weeks apart) or lymphoma protocol (4x375mg/m2-1 week apart). In two systematic reviews, the lymphoma protocol showed better clinical outcomes and a lower relapse risk. We therefore chose the lymphoma protocol to which she responded successfully. Ahmed and Shetty reviewed the results of 499 patients with all forms of treatment refractory PV who had been treated with RTX. Clinical remission was observed in 90-95% of patients within 6 weeks, and complete resolution was observed within 3 to 4 months. According to Tavakolpour et al, the majority of patients responded well to RTX therapy with an expected relapse following 6 to 10 months after the therapy. Ahmed and Shetty also reported the incidence of relapse to be 50-80%. Similarly, Kim et al also observed a relapse rate of 76% with a median time of 17 months. In PV, recurrences might be due to reappearance of pathogenic autoantibody producing B-cells which could be hidden in immune privileged sites, rather than hematopoietic stem cell recovery. Therefore some authors favor maintenance dosing to prolong remission and prevent recurrences. Other researchers however refute this approach and suggest that further infusions should be saved just for the refractory recurrences. It was reported that relapse was associated with CD19+B-cell repopulation, low CD4+T-cell count and positive anti-Dsg1 and Dsg3 testing. These parameters were suggested for predicting relapse after RTX treatment. Vinay et al reported three oral refractory PV patients, who received intralesional RTX and showed clinical remission at 1 and 16 weeks. During follow-up periods of 6 months, only one patient relapsed, and no serious adverse effects were recorded. One should keep in mind that RTX treatment showed a high relapse rate, and therefore intralesional RTX injection could be a good option for our patient in case of relapse. However, 20-month after the RTX ‘treatment,’ our patient remains in remission and her follow-up CD19+B-cell count one-year later is within normal range. The long-term remission in our case is most probably achieved by using the lymphoma protocol and maintenance of conventional immunosuppressants using low dosages.
The most common side effects of RTX therapy is bacterial and viral infections which could lead to death. Serious adverse effects (i.e. infection and septicemia) were reported to be seen in 4.8% and 2.1% of the patients in the lymphoma and RA protocols respectively. Although the treatment was administered according to the lymphoma protocol, our patient did not develop any serious side effects. RTX is an effective treatment of PV, but unfortunately, its use is restricted due to exorbitant costs. However, a 30.3% decrease in the medication and hospital associated costs in comparison to 6 months before and 6 months after RTX treatment of pemphigus and pemphigoid disorders was reported. Additionally, the improvement of the patient's quality of life with RTX has been priceless. Our patient had refractory oral PV and she was successfully treated with RTX without any life threatening side-effects. RTX improves patient's symptoms and quality of life. It appears safe and an effective treatment method particularly in refractory cases of PV. The cost is a major challenge with its use; therefore, medical schemes and hospital therapeutic committees should find ways to urgently reduce cost.

REFERENCES:


