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Clinical resolution of pemphigus vulgaris on rituximab

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Abstract

Although significant progress has been made in the treatment of pemphigus vulgaris (PV) with rituximab (RTX), a consensus remains to be determined for standard treatment protocol regarding optimal dosing, infusion regimen, and use of concomitant immunotherapy to achieve safe, effective, and rapid clinical response. We describe a patient with pemphigus vulgaris treated with high dose rituximab with the rheumatoid arthritis protocol along with intravenous immunoglobulin therapy. This case provides evidence towards the growing body of research needed to modify and improve treatment for pemphigus using rituximab.

Keywords: pemphigus vulgaris, rituximab, rheumatoid arthritis protocol, intravenous immunoglobulin therapy, dosing regimen, treatment protocol

Introduction

Pemphigus vulgaris (PV) is an autoimmune blistering disease that involves the skin and mucous membranes. Treatment of this potentially fatal condition with systemic corticosteroids and immunosuppressive therapy presents a challenge owing to the complications associated with their long-term use. More recently, treatment with rituximab (RTX), a chimeric, monoclonal antibody that targets the CD-20 molecule on the surface of B-cells, has allowed clinicians to induce early clinical remission while reducing the dose of concomitantly used prednisone and immunosuppressive therapy [1].

Although significant progress has been made for treatment of PV using RTX, no consensus has been reached on RTX protocol, regarding optimal dosing, infusion regimen, and use of concomitant intravenous immunotherapy (IVIG) to achieve safe, effective, and rapid clinical response with minimal side effects. The treatment protocol of RTX for non-Hodgkin lymphoma (LP) was originally used for patients with PV. However, upon the development of the rheumatoid arthritis protocol (RAP), clinicians are increasingly and more widely using this for PV patients because of the similarity in mechanism of the two autoimmune disorders. The RAP is defined as one cycle of either 500 mg or 1000 mg given as an infusion on days 1 and 15 [1]. To date, no standard treatment protocol exists for clinicians regarding the use of high dose or low dose RTX with RAP. It has also not been determined whether a modified RAP with concomitant therapy, such as intravenous immunoglobulin therapy (IVIG), is beneficial. The purpose of this report is to provide evidence in support of the modified RAP protocol to advance current understanding of this treatment regimen to be utilized by clinicians while treating patients with PV in the future.

Case synopsis

A 75 year old man with recent diagnosis of pemphigus vulgaris (PV) treated with modified Rheumatoid Arthritis Protocol (RAP) with high dose intravenous immunoglobulin therapy (IVIG) obtained clinical remission in six weeks off therapy and effectively achieved complete clinical resolution in three months off therapy without adverse events. After inadequate response to an initial eight weeks of conventional immunosuppression therapy with systemic corticosteroids and mycophenolate mofetil, treatment with the modified RAP protocol was initiated. This consisted of 2 infusions of 1g Rituximab 15 days apart over one month, with concomitant

intravenous immune globulin, 2g per kilogram of body weight. During treatment, he continued to receive conventional immunosuppression with 50mg prednisone daily and mycophenolate mofetil 1.5g twice daily. This regimen was well-tolerated without major side effects or morbidity. One week after completing the second infusion, our patient noted marked improvement. Mycophenolate mofetil was discontinued and prednisone was subsequently weaned by 50% every 4 weeks. Six weeks after the second RTX infusion, the patient achieved clinical remission. Skin examination revealed over 90% of lesions resolved, with a few remaining flaccid bullae and pustules. Eight weeks after RAP completion, desmoglein-specific autoantibodies remained elevated with desmoglein AB3 at 132, while circulating B cells remained undetectable with 0% lymphocytes expressing CD19 phenotype and 0% express CD 20 phenotype. There were decreased levels of lymphocytes consistent with recent immunomodulatory treatment, including CD4: 295, CD19 <20, CD3 367, absolute lymphocytes 674. By three months post-RAP completion, our patient completed the prednisone taper, discontinued use of all immunosuppressive drugs, and maintained complete clinical remission of PV.

Discussion

This case highlights the successful treatment of severe of pemphigus vulgaris (PV) in a recently diagnosed male without significant comorbidities using high dose modified Rheumatoid Arthritis Protocol (RAP) with high dose intravenous immunoglobulin therapy (IVIG) to induce rapid short term remission in six weeks off therapy and resolution in three months off therapy without the need for additional therapy. The decision to utilize the RAP to administer rituximab (RTX) in this patient is supported by evidence from an analysis comparing rituximab treatment of lymphoma protocol (LP) with RAP [1]. In this analysis, a larger number of patients achieved clinical remission off therapy in the RAP group compared to the LP group, and more patients in the LP required additional use of corticosteroids and immunosuppressive adjunctive therapy compared to the RAP group [1]. This analysis reported clinical remission on RAP in 90%-95% of patients within less than six weeks and a complete resolution within three to four months, as was observed in our patient [1].

There is an emerging debate about the optimal dose of RTX in patients who are treated with RAP regarding the efficacy and safety of higher doses (1000 mg), [6]. The dosage of RTX carries significant clinical implications since RTX can suppress natural immunity by decreasing the levels of B-cells and the immunoglobulin IgM [4]. In comparisons of outcomes in patients treated with 1000 mg RTX versus 500 mg, a significantly higher number of patients in the 1000 mg group were off all therapies after RTX treatment [5]. Moreover, the relapse rates were higher in the low dose group. Despite the efficacy of high dose RTX, studies in the 1000 mg group show 2.1% morbidity related to medication and 1% of the patients died. No drug related morbidity or deaths were reported in the 500 mg group [5]. This greater risk of infection poses a challenge.

Despite concern for adverse side effects from immunosuppression on higher doses of RTX, no observable side effects were associated with the use of high dose rituximab in our patient. Our case supports recent evidence that suggests the prognosis and outcomes of RAP improve with intravenous immunoglobulin (IVIG) by preventing the complications associated with immunosuppression from high dose RTX. IVIG maintains healthy immunity by providing protection from reduced immunoglobulin levels, while rituximab eliminates pathogenic B cells and autoantibodies [2].

Our case further supports the growing body of evidence that there is a synergism to RTX and IVIG treatment relating to IVIG's ability to accelerate catabolism of pemphigus autoantibodies [3]. The short-term remission and lack of need for additional immunosuppressive therapy in our patient may be attributable to the elimination of B cells by RTX in combination with the regulatory effects of IVIG.

Of note, the PV titers remained elevated post treatment. This has been documented in previous studies of patients with a complete remission after RTX therapy [1]. Elevated levels of circulating autoantibodies should not be viewed in isolation as negative predictive factors of therapeutic response to RTX. Rather, clinical improvement and downward trend of titers is indicative of response to treatment, as demonstrated by this patient.

Conclusion

Our case suggests that high dose modified Rheumatoid Arthritis Protocol (RAP) of rituximab (RTX) with high dose intravenous immunoglobulin therapy (IVIG) offers a promising successful therapeutic option for pemphigus vulgaris (PV). This case is relevant to report in a time of great uncertainty regarding the optimal RTX treatment approach. Although RTX has significantly advanced the treatment of PV, a consensus on the ideal protocol remains to be determined. This report adds to the growing body of research needed to modify and improve treatment for PV using RTX.

References

1. Ahmed, A. R., & Shetty, S. (2015). A comprehensive analysis of treatment outcomes in patients with pemphigus vulgaris treated with rituximab.*Autoimmunity reviews*, 14(4), 323-331. [PMID:25499920].
2. Ahmed, A. R., Spigelman, Z., Cavacini, L. A., & Posner, M. R. (2006). Treatment of pemphigus vulgaris with rituximab and intravenous immune globulin. *New England Journal of Medicine*, 355(17), 1772-1779. [PMID: 17065638].
3. Ahmed, A. R., & Dahl, M. V. (2003). Consensus statement on the use of intravenous immunoglobulin therapy in the treatment of autoimmune mucocutaneous blistering diseases. *Archives of dermatology*, 139(8), 1051-1059. [PMID: 12925395].
4. Cho, H. H., Jin, S. P., & Chung, J. H. (2014). Clinical experiences of different dosing schedules of rituximab in pemphigus with various disease severities. *Journal of the European Academy of Dermatology and Venereology*, 28(2), 186-191 [PMID: 23356542].
5. Kanwar, A. J., Vinay, K., Sawatkar, G. U., Dogra, S., Minz, R. W., Shear, N. H.,... & Hashimoto, T. (2014). Clinical and immunological outcomes of high-and low-dose rituximab treatments in patients with pemphigus: a randomized, comparative, observer-blinded study. *British Journal of Dermatology*, 170(6), 1341-1349. [PMID: 24640990].
6. Leshem, Y. A., Hodak, E., David, M., Anhalt, G. J., & Mimouni, D. (2013). Successful treatment of pemphigus with biweekly 1-g infusions of rituximab: a retrospective study of 47 patients. *Journal of the American Academy of Dermatology*, 68(3), 404-411. [PMID: 23044076].