International Journal of Healthcare Sciences ISSN 2348-5728 (Online)
Vol. 11, Issue 2, pp: (30-33), Month: October 2023 - March 2024, Available at: www.researchpublish.com

Efficacy of Corticosteroid Versus Rituximab For Pemphigus Vulgaris: A Literature Review

Elrica Stella Octaviani[1], Arin Armini[2], Luh Putu Dina Wahyuni[3]

[1]Faculty of Medicine, University of North Sumatera, Medan, North Sumatera, Indonesia

[2] Faculty of Medicine Maranatha, Bandung, West Java, Indonesia

[3]Department of Dermatology and Venereology, Bali Mandara General Hospital, Denpasar, Bali, Indonesia

DOI: https://doi.org/10.5281/zenodo.10065763

Published Date: 02-November-2023

Abstract: **Pemphigus Vulgaris (PV) is a mucocutaneous blistering disorder characterized by pathogenic autoantibodies against desmogleins 1 and 3. The etiology of pemphigus vulgaris is unknown, but patients are at risk that has a genetic predisposition. Several studies have linked PV with human leukocyte antigen (HLA). In addition to diet, stress, viral infections, medications, radiation therapy, and allergens, environmental factors may induce immune dysregulation, leading to a flare of PV. Systemic corticosteroids have significantly impacted the treatment of pemphigus vulgaris and remain the backbone in the management of PV. Anti-CD20 monoclonal antibodies, such as rituximab and ofatumumab, have also been used with corticosteroids for first-line treatment in moderate-to-severe pemphigus. This study aims to review the efficacy of corticosteroid (CS) versus rituximab for PV.**

Keywords: **Corticosteroid, Efficacy**, **Pemphigus Vulgaris, Rituximab.**

I. INTRODUCTION: PEMPHIGUS VULGARIS AND ITS TREATMENT

Pemphigus Vulgaris (PV) is a mucocutaneous blistering disorder characterized by pathogenic autoantibodies against desmogleins (Dsg) 1 and 3.[1] PV is a rare disease that causes blisters on cutaneous and mucosal surfaces. The mean age of onset is 50 to 60 years of age, and it affects both sexes equally.[2] PV is a rare disease. The prevalence in various studies is 0.005% to 0,009%. The average age of onset is 50 to 60 years, and it affects both sexes equally.[3] Although PV is not as contagious as initially thought, there have been possible triggers identified that might induce PV in patients with other autoimmune disorders.[3] The etiology of pemphigus vulgaris is unknown, but patients are at risk that has a genetic predisposition. Several studies have linked PV with human leukocyte antigen (HLA). In addition to diet, stress, viral infections, medications, radiation therapy, and allergens, environmental factors may induce immune dysregulation, leading to a flare of PV.[2]

PV is caused by autoantibodies that target keratinocyte proteins (desmogleins). Initial lesions consist of cell detachment (acantholysis) in the deep part of the epithelium, just above the basal layer (suprabasal acantholysis), resulting in a splitting that gives rise to blister formation (intraepithelial bulla). In two-thirds of cases, the oral mucosa is the site of onset, and the disease may remain confined there for several months. Multiple mechanisms for antibody-induced acantholysis have been suggested, including the induction of signal transduction and the inhibition of adhesive molecule function through steric hindrance, which can trigger cell separation.[2] Lesions often appear on the trunk, intertriginous areas (axillar, inframammary, and inguinal regions), and scalp, but every site may be involved. Pruritus and the degree of pain are variable. Other stratified squamous epithelial mucosal surfaces (pharynx, larynx, esophagus, conjunctiva, urethra, cervix, and anal mucosa) also may be affected in patients with more severe disease. If left untreated, PV becomes generalized (new crops of bullae appear anywhere, and more areas of skin present eroded and crusted), the outcome often being fatal within 1 to 3 years due to uncontrolled fluid and protein loss or opportunistic infection.[4]

Systemic corticosteroids have significantly impacted the treatment of pemphigus vulgaris and remain the backbone in the management of PV. The first-line treatment of mild PV is systemic corticosteroids, which take several weeks to achieve a response.[2] Tapering down of the dose can be initiated when symptoms are improved, but if there are more than three lesions reappearance occurs, dosing should be increased again to induce remission.[5] The most often used oral corticosteroid is prednisone, prednisolone, and deflazacort.[6] The efficacy of steroid-sparing medications, most frequently azathioprine, mycophenolate mofetil (MMF), rituximab, methotrexate, intravenous immunoglobulin (IVIg), and cyclophosphamide, has been the focus of a lot of recent studies.[7]

The second-line treatment combines corticosteroids and adds azathioprine or mycophenolate mofetil (MMF). Azathioprine is a purine analog that inhibits purine synthesis. It can be administered orally or by intravenous infusion. Azathioprine should be discontinued if no improvements are seen within three months.[8] MMF functions as an immunosuppressant by inhibiting purine synthesis. It can be administered orally or by intravenous infusion. MMF is usually effective within two months of initiating treatment.

Anti-CD20 monoclonal antibodies, such as rituximab and ofatumumab, have also been used with corticosteroids for first-line treatment in moderate-to-severe pemphigus. Rituximab is an anti-CD20 monoclonal antibody that stops B lymphocytes from maturing into autoantibody-producing plasma cells. It is administered intravenously, and response is usually seen within three months.[8] Systemic corticosteroids and other immunosuppressants have long been the basis of therapy for pemphigus vulgaris despite being very difficult to treat.[9] This study aims to review the efficacy of corticosteroid (CS) versus rituximab for PV.

II. EFFICACY OF CORTICOSTEROIDS VERSUS RITUXIMAB FOR PEMPHIGUS VULGARIS

A. Corticosteroids

PV treatment is intended to initiate and maintain remission, which clinically equates to stopping new vesicle growth, healing previous erosions, and the end of treatment tapering to maintenance dosages. The difficulty lies in preventing relapse over the long term and avoiding the adverse effects of repeated corticosteroid and immunosuppressive therapy.[5] The most well-established therapy for the treatment of PV is systemic corticosteroids Results have improved over time, and current research indicates that complete remission rates on low-dose corticosteroids (prednisolone 10 mg or fewer per day) are 52-76% at one year, with a small percentage of deaths.[10] When corticosteroids interact with the cytoplasmic corticosteroid receptor, the expression of anti-inflammatory proteins is upregulated, and the expression of pro-inflammatory proteins is downregulated. The cytoplasmic corticosteroid receptor that the unbound corticosteroid attaches to causes it to move into the nucleus, forming a dimer that binds to corticosteroid-response elements in the promoter region of specific genes. The unbound corticosteroid penetrates cells and causes its effects by doing this.[5]

Early studies recommended high doses, such as prednisolone starting doses of 120-400 mg daily. Once remission is achieved and maintained, the corticosteroid dose can be gradually reduced with recovery of the majority of lesions, both cutaneous and oral. Continuous treatment should be considered during relapse, in addition to increasing corticosteroid doses, because relapses may occur when corticosteroid doses are decreased again. If the present adjuvant treatment has been given at an adequate dose for at least 3 months, it may be appropriate to add an adjuvant drug, increase the dose of an existing adjuvant, or switch to an alternative. Following the recommendations for preventing corticosteroid-induced osteoporosis is highly advised. For those under 40, a prednisolone dose of 7.5 mg for at least three months is considered a risk factor. For people over 40, any dose is seen as a risk factor.[10] Much recent research on pemphigus has focused on discovering the best steroid-sparing treatment because of the adverse effects of long-term systemic corticosteroids, such as hypertension, diabetes mellitus, osteoporosis, and ophthalmic problems.[7]

B. Rituximab

By successfully treating paraneoplastic pemphigus in a patient with follicular non-Hodgkin lymphoma, Heizmann M et al. published the first study on using rituximab in pemphigus.[11] For moderate to severe pemphigus vulgaris, rituximab has emerged as one of the most promising targeted treatments, generating clinical remission within 1-3 months following therapy commencement. Rituximab is now recommended as first-line therapy for patients with moderate to severe pemphigus despite its previous use as second or third-line therapy.[1] Rituximab is a monoclonal humanized antibody that targets the CD20 cell surface antigen found on B cells.[5] Depletion of B cells, which decreased anti-Dsg1 and anti-Dsg3 autoantibodies, supported rituximab's mode of action in PV. In PV patients, rituximab is well tolerated and has a steroid-sparing effect.[12]

Early use of rituximab in treating pemphigus leads to improved outcomes, such as higher remission rates, a more extended period without the disease, a lower rate of relapse, and a significant decrease in the need for corticosteroids.[11] According to the European Dermatology Forum (EDF) recommendations, rituximab is advised for patients requiring>10 mg of prednisolone in addition to an immunosuppressive adjuvant.[5] According to the study's findings by Josko et al., rituximab is generally well tolerated and successful in achieving remission in pemphigus patients. The potential of rituximab to drastically reduce corticosteroid administration and side effects associated with corticosteroids makes it crucial for pemphigus patients.[13]

There were no patients treated with rituximab in the Anandan et al. research who experienced any immediate adverse effects that were life-threatening. While receiving the infusion, 10% of the patients experienced bradycardia and hypotension, successfully treated by reducing the infusion rate. During follow-up, 20% of patients got herpes labialis, one had erythema nodosum, one acquired pulmonary tuberculosis, and two developed onychomycosis. Anandan et al. considered these as potential adverse effects because they happened during the follow-up period following rituximab infusion and were not noticed in the patients when they were receiving Dexamethasone Cyclophosphamide Pulse (DCP) treatment.[14]

C. Corticosteroids or Rituximab

A study by Chen et al. showed that at month 24, 34 of 38 patients (90%) on rituximab plus prednisone achieved complete remission (CR) off corticosteroids (CRoff) ≥ 2 months vs. 10 of 36 patients (28%) on prednisone alone. Although more patients on the rituximab plus prednisone than on the prednisone alone developed significant infections, these infections could be treated and did not force patients to stop receiving their medication.[12]

A trial by Morgado et al. showed the efficacy of rituximab combined with low-dose prednisone (RTX-LDPRD) compared with long-term high-dose prednisone as monotherapy (HD-PDN). At 24 months, significant outcomes were seen: 34% of patients in the HD-PRD group and 89% of those in the RTX-LDPRD group had achieved complete remission without treatment (CR-WT). As a result of the trial's findings, corticosteroid medication may no longer be the first-line treatment for pemphigus, with rituximab taking its place.[15]

Systemic corticosteroids are first-line therapy for mild, moderate, and severe PV. Similarly, rituximab is a first-line treatment for mild, moderate, and severe PV. This medication can be taken alone or in combination with others.[16] Rituximab reduced the need for further steroids and other immunosuppressants while successfully treating pemphigus vulgaris. It was also superior to standard care and resulted in longer-lasting remissions. Rituximab was more efficient when administered early in the progression of the disease.[14] Rituximab offers various benefits for treating pemphigus vulgaris.

III. CONCLUSION

PV is a mucocutaneous blistering disorder caused by autoantibodies that target keratinocyte proteins (desmogleins). If left untreated, PV becomes generalized (new crops of bullae appear anywhere, and more areas of skin present eroded and crusted), the outcome often being fatal within 1 to 3 years due to uncontrolled fluid and protein loss or opportunistic infection. Systemic corticosteroids are first-line therapy for mild, moderate, and severe PV. Similarly, rituximab is a first-line treatment for mild, moderate, and severe PV. This medication can be taken alone or in combination with others. Long-term systemic corticosteroids may have side effects in the future, including osteoporosis, diabetes mellitus, hypertension, and trouble with vision. Rituximab reduced the need for further steroids and other immunosuppressants while successfully treating pemphigus vulgaris. It was also superior to standard care and resulted in longer-lasting remissions. Rituximab offers various benefits for treating pemphigus vulgaris and more efficient when administered early in the progression of the disease. However, according to our literature analysis, rituximab and prednisone work better together than prednisone or rituximab does on its own.

REFERENCES

[1] Agarwal, R. P. Hall, L. L. Bañez, and A. R. Cardones, “Comparison of rituximab and conventional adjuvant therapy for pemphigus vulgaris: A retrospective analysis,” PLoS One, vol. 13, no. 9, p. e0198074, Sep. 2018, doi: 10.1371/journal.pone.0198074.

[2] J. Ingold and M. A. Khan, Pemphigus Vulgaris. StatPearls Publishing, 2023.

[3] S. Wertenteil, A. Garg, A. Strunk, and A. Alloo, “Prevalence Estimates for Pemphigus in the United States,” JAMA Dermatology, vol. 155, no. 5, p. 627, May 2019, doi: 10.1001/jamadermatol.2018.5954.

[4] M. Wardhana and L. Rusyati, "PREVALENCE AND QUALITY OF LIFE OF PEMPHIGUS PATIENTS AT SANGLAH GENERAL HOSPITAL BALI-INDONESIA," Bali Med. J., vol. 2, Jan. 2013, doi: 10.15562/bmj.v2i1.38.

[5] K. Kridin, "Emerging treatment options for the management of pemphigus vulgaris," Ther. Clin. Risk Manag., vol. Volume 14, pp. 757–778, Apr. 2018, doi: 10.2147/TCRM.S142471.

[6] A. M. Porro, C. A. Seque, M. C. C. Ferreira, and M. M. S. e S. Enokihara, "Pemphigus vulgaris," An. Bras. Dermatol., vol. 94, no. 3, pp. 264–278, May 2019, doi: 10.1590/abd1806-4841.20199011.

[7] B. S. Daniel and D. F. Murrell, "Management of pemphigus," F1000Prime Rep., vol. 6, May 2014, doi: 10.12703/P6-32.

[8] Bilgic and D. F. Murrell, "What is novel in the clinical management of pemphigus," Expert Rev. Clin. Pharmacol., vol. 12, no. 10, pp. 973–980, Oct. 2019, doi: 10.1080/17512433.2019.1670059.

[9] S. Das, K. Agarwal, S. Singh, D. Halder, S. Sinha, and A. De, "A comparative study to evaluate the efficacy and cost of rituximab versus dexamethasone cyclophosphamide pulse in patients of pemphigus vulgaris," Indian J. Dermatol., vol. 66, no. 2, p. 223, 2021, doi: 10.4103/ijd.IJD_306_20.

[10] K. E. Harman et al., "British Association of Dermatologists' guidelines for the management of pemphigus vulgaris 2017," Br. J. Dermatol., vol. 177, no. 5, pp. 1170–1201, Nov. 2017, doi: 10.1111/bjd.15930.

[11] Hassan, F. Rehman, S. Sultan, A. Aslam, I. Tasaduq, and S. Reyaz, "Rituximab in Pemphigus – An Observational Study from a Tertiary Care Center of North India," Indian Dermatol. Online J., vol. 13, no. 5, p. 620, 2022, doi: 10.4103/idoj.idoj_170_22.

[12] M. Chen et al., "Rituximab is an effective treatment in patients with pemphigus vulgaris and demonstrates a steroid-sparing effect," Br. J. Dermatol., vol. 182, no. 5, pp. 1111–1119, May 2020, doi: 10.1111/bjd.18482.

[13] Miše, I. L. Jukić, and B. Marinović, "Rituximab - Progress but Still Not a Final Resolution for Pemphigus Patients: Clinical Report From a Single Center Study," Front. Immunol., vol. 13, May 2022, doi: 10.3389/fimmu.2022.884931.

[14] V. Anandan, "Rituximab: A Magic Bullet for Pemphigus," J. Clin. DIAGNOSTIC Res., 2017, doi: 10.7860/JCDR/2017/21868.9717.

[15] Morgado-Carrasco, P. Giavedoni, X. Fustà-Novell, and P. Iranzo, "Rituximab: Revolutionizing the Treatment of Pemphigus," Actas Dermo-Sifiliográficas (English Ed., vol. 109, no. 2, pp. 177–178, Mar. 2018, doi: 10.1016/j.adengl.2017.12.015.

[16] P. Joly et al., "Updated S2K guidelines on the management of pemphigus vulgaris and foliaceus initiated by the european academy of dermatology and venereology (EADV)," J. Eur. Acad. Dermatology Venereol., vol. 34, no. 9, pp. 1900–1913, Sep. 2020, doi: 10.1111/jdv.16752.