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Rituximab Therapy for Persistent, Severe and Extensive Idiopathic Bullous Pemphigoid

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Abstract

Background: Idiopathic Bullous Pemphigoid (IBP) is a rare blistering autoimmune disease. Its morbidity and mortality have remained high owing to complications of extensive skin involvement as well as its conventional steroid therapy. We reviewed the medical literature and found indicators of an autoimmune etiology for its pathogenesis triggering genetically predisposed patients. **Objective**: to evaluate, prospectively, the role of Rituximab (R) therapy in its persistent, severe and extensive form. **Patients and methods**: A total of 12 patients, with disease duration of 6 ± 1 months, were treated with yearly R infusions (1 g followed by 1 g 2 weeks later). **Results**: Significant clinical improvement was achieved as documented by decrease in total score of Bullous Pemphigoid Disease Area Index from 60 ± 3 to 6 ± 2 that persisted for 26 ± 11 months of follow up. Moreover, IBP autoantibodies (anti-BP 180 and anti-320 IgG) levels fell from to 91 ± 3 and 81 ± 2 to 8 ± 2 and 9 ± 2, respectively. **Conclusions**: R is a safe and effective treatment for severe IBP and such response further confirms its autoimmune pathogenesis.

Keywords

Bullous Pemphigoid, Rituximab, Treatment, BP Autoantibodies, Bullous Pemphigoid Disease Area Index

1. Introduction

Idiopathic Bullous pemphigoid (IBP) is an uncommon autoimmune bullous disorder, with significant morbidity and mortality. It has an incidence rate of 3/100,000 person-years yet a high mortality at 23.5% in the first year after diagnosis [1]. It is predominantly a disease of the elderly, and is associated with significant health care costs [2]. Its morbidity and mortality have remained high owing

to complications of extensive skin involvement as well as its conventional steroid therapy, such as pneumonia, septicemia, and cardiovascular disease. Hence; early selection of safe and effective immunosuppressive therapy and control of such comorbidities are crucial in its management. In severe forms, systemic corticosteroid therapy (prednisone 0.5 mg/kg/day) is indicated [3]. For maintenance treatment, doses may be tapered gradually within 4 to 6 months of initiation of treatment. Adjunctive therapy included its combination with azathioprine, mycophenolate mofetil, tetracyclines plus nicotinamide, methotrexate, and dapsone [4]. On the other hand; Rituximab (R) is the only drug to gain European Medicine Agency and US Food and Drug Administration approval for the treatment of Pemphigus Vulgaris (PV) with dramatic efficacy and safety as a first line therapy [5]. However, in IBP, the available data are scarce and reflect ambiguous efficacy [6]. In the current study, we prospectively, evaluated the early role of Rituximab in the induction phase, of severe IBP, and as the sole drug in its maintenance phase for >2 years.

2. Patients and Methods

Patients with refractory IBP who attended or were referred to Prof/El-Reshaid medical clinic, between 1st January 2019 and 31st December 2022, were selected for treatment with R. The clinic was established in 1997 in the center of Kuwait City and has adequate diagnostic and therapeutic facilities to care for out-patients and in-patients with its affiliated hospitals. Patients were included if they had: 1) age > 14 years; 2) BP diagnosed clinically and confirmed by histopathological examination that shows subepithelial clefts with eosinophilic spongiosis and IgG and/or C3 deposition along the dermal-epidermal junction on direct Immunofluorescence and high titers of autoantibodies directed to components of the basement membrane (BP antigens BP180 and BP230); 3) persistent disease for >3 months after systemic Corticosteroid therapy or relapsing disease despite treatment with Corticosteroids 4) severe and extensive BP disease with Bullous Pemphigoid Disease Area Index > 46; 5) no evidence of recent or recurrent exposure to solar or traumatic injuries, primary skin infections, HIV, drugs viz. antibiotics (Sulfasalazine, Quinolones, Cephalosporines), NSAIDs, Antihypertensives (Betablockers and ACEI), diuretics (Furosemide and Spironolactone), Penicillamine, Gliptins, Lithium, Neuroleptic agents, Amiodarone, Biological agents and NSAIDs.

Initially, all patients were treated, as burn cases, with intravenous fluids with/without human albumin to control shock-state and replace the deficient electrolytes. They also had received broad-spectrum antibiotics to protect against skin and chest infections as well as topical treatments. After control of local and systemic infections; they had received Solumedrol (Methylprednisolone sodium succinate) 1 g infusion, over 1 hour, for 3 days followed by Prednisone 1 mg/kg/day for 2 weeks that was tapered down and discontinued by 6 weeks. Moreover, they had received 1 g of Rituximab infusion, over 4 - 6 hours, followed by another 1 g

2 weeks later. The R dose was repeated on yearly basis as a sole maintenance therapy to prevent future relapses. After their initial in-hospital stabilization, patients were assessed every 2 weeks as outpatients for 6 weeks. They were assessed clinically using Bullous Pemphigoid Disease Area Index (BPDAI) scores and with laboratory tests that included complete blood count as well as renal and liver function tests. After 6 weeks of stabilization; patients were seen on monthly basis. The same dose of R was given on yearly basis.

2.1. Assessment of Severity of IBP

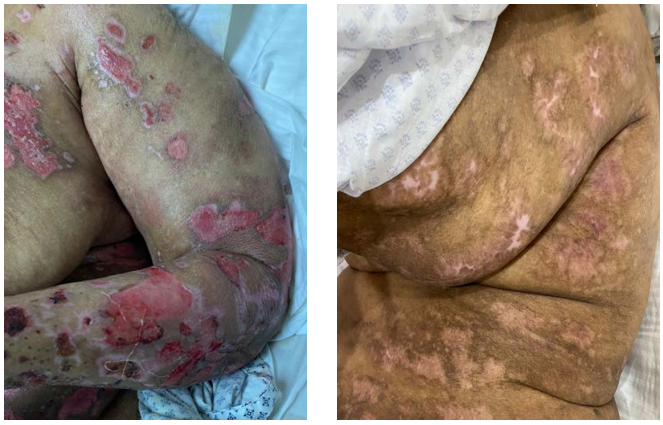
The severity of the disease and its response to therapy was assessed using the Bullous Pemphigoid Disease Area Index (BPDAI) score system. The extent of the disease was calculated as Total Activity Score (TAS) that included sum of; 1) severity of infiltration/papulation (none, 0; mild, 1; moderate, 2; severe, 3) multiplied by body surface area affected (0%, 0; 1% - 9%, 2; 10% - 29%, 3; 30% - 49%, 4; 50% - 69%, 5; 70% - 89%, 6; 90% - 100%, 7) at head, trunk, upper extremities and lower extremities; 2) Numerical rating scale of pruritis (0 - 30). TAS expressed disease activity as: 0 - 1, near remission; 2 - 6, mild; 7 - 15, moderate; 16 - 33, severe; 34 - 46, most severe.

2.2. Statistical Analysis

SPSS statistical package version 25 was used for data entry and processing. The p-value ≤ 0.05 was used as the cut-off level for significance. Since all variables were normally distributed; they were expressed as mean ± SD and compared using student's t-test. Comparison of changes with time, following therapy, was by done using ANOVA test for repeated measures.

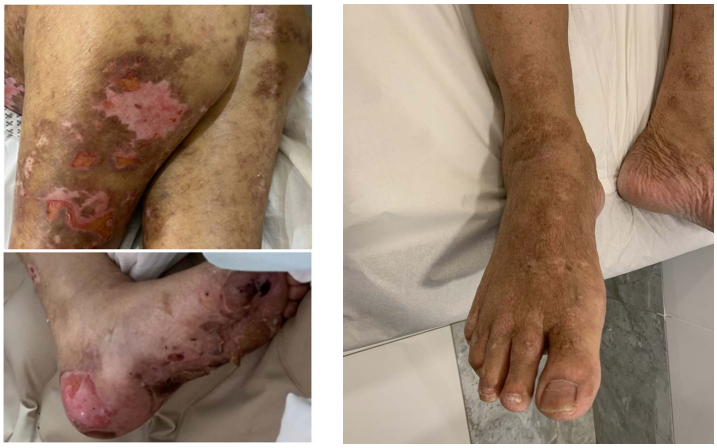
3. Results

A total of 13 patients were recruited in the study, yet 1 patient was excluded, at entry, for severe allergic reactions to R. The 12 study-population were elderly whites at 65 ± 4 years, of whom 7 (58%) were females. They had persistent disease for 5.5 ± 1 months prior to inclusion time. As shown in Table 1; all patients, at start, had severe disease with TAS at 60 ± 3 and high IgG autoantibodies (Anti-BP 180 at 91 ± 3 U/ml and Anti-BP 320 at 81 ± 2). By 6 weeks; most lesions had healed significantly with decrease of TAS to 22 ± 4 and titers of autoantibodies to 17 ± 2 and 16 ± 2, respectively. By the end of the study; all patients were stable for >1 year and up to 4 years with a mean duration of follow up at 26 ± 11 months. The final TAS score was 6 ± 2 and autoantibodies titers at 8 ± 2 and 9 ± 2, respectively. All those changes were significant at <0.00001. Figures 1-3 show the dramatic improvement in different body area (arms, legs/feet and back), in some patients, following R therapy. As stated only 1 patient had significant immediate allergic reaction to R-infusions and was excluded from analysis yet none of the included patients had side effect of R-therapy. Moreover, on follow up; there was no significant disease relapses or hematological, neurological, hepatic and renal complications.



(a) (b)

Figure 1. Arm lesions before (a) and after Rituximab treatment (b).



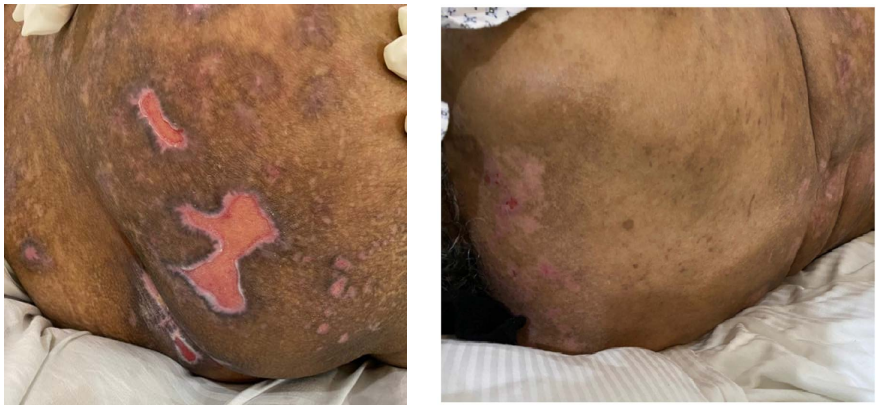
(a) (b)

Figure 2. Leg and feet lesions before (a) and after Rituximab treatment (b).

Table 1. Response to Rituximab in patients with idiopathic Bullous Pemphigoid.

Parameter	Assessment*		
	At start	After 6-weeks	Final
A-BPDAI scores:**			
Skin lesions	42 ± 3	16 ± 4	3 ± 1
Pruritus' component	16 ± 1	6 ± 2	3 ± 1
Total activity (TAS)	60 ± 3	22 ± 4	6 ± 2
BP IgG Autoantibodies*:**			
Anti-BP180	91 ± 3	17 ± 2	8 ± 2
Anti-230	81 ± 2	16 ± 2	9 ± 2

* $p < 0.00001$ between at start, after 6-weeks and final assessment. ** BPDAI: Bullous Pemphigoid Disease Activity Score & TAS: total activity score; A-Skin lesions score is up to 120 and pruritus up to 30; B-TAS: 0 - 1, Near remission; 2 - 6, mild, 7 - 15, moderate, 16 - 33, severe; 34 - 46, most severe. *** Anti-BP IgG 190 & 320 are negative if <20.



(a) (b)

Figure 3. Back lesions before (a) and after Rituximab treatment (b).

4. Discussion

Autoimmune bullous disorders are rare blistering skin disorders characterized by the production of autoantibodies against adhesion molecules of the skin viz. desmosomal proteins in PV and components of the hemidesmosomes in (IBP) [7]. The clinical skin manifestations of these 2 diseases are similar yet PV usually manifest with severe disease with early involvement of oral and anogenital areas. Diagnosis, of both, is based on clinical manifestations and is confirmed by histological, immunofluorescence, and ELISA serological testing [8]. On histology; PV is characterized by intraepithelial cleft and acantholysis while BP by subepithelial clefts and blisters with eosinophilic spongiosis. Direct Immunofluorescence confirms the site involvement for both disorders viz. IgG deposition at the keratinocyte cell membrane in PV and IgG and/or C3 along the dermal-epidermal junction in BP. Prior to inclusion in the study, detailed past history excluded drug-induced bullous disorders [9]. Moreover, histopathological examination and serological testing complemented clinical assessment in excluding other skin diseases with potential bullous manifestations viz. PV, epidermolysis bullosa acquista, bullous lupus erythematosus, dermatitis herpitiformis, linear IgA bullous disease and porphyria cutanea tarda [10]. Previous studies have shown an autoimmune pathogenesis in IBP viz. 1) skin deposition of immunoglobulins, 2) high titers of bullous pemphigoid antigen-specific IgG autoantibodies, and 3) positive response to Corticosteroids [3] [4] [6] [7] [8]. Moreover, others have shown a genetic susceptibility to the disease via its association with certain HLA alleles (HLA-DRβ1 * 04, HLA-DRβ1 * 1101 and HLA-BDB1 * 0302) that facilitate antigen presentation of basement membrane zone (BMZ) antigens to T cells and hence starts of autoimmunity process [11]. Triggering factors include; solar or traumatic injuries, primary skin infections, HIV, drugs [12]. Moreover, the pathogenic role of IgE in the development of IBP is endorsed by the finding of; 1) IgE deposition in the basement membrane zone in patients with BP and 2) positive correlation between serum levels of IgE autoantibodies against BP180 and BP disease activity [13]. All those factors were the basis for the use Ritux-

imab in our patients. The drug is a chimeric human/mouse monoclonal antibody that was approved in USA since 1997 for treatment of non-Hodgkin lymphoma and recently for severe rheumatoid arthritis and glomerulopathy [14]. It binds to CD20 antigen expressed on normal differentiated B-lymphocytes and pre-B-cells. Unlike other murine monoclonal antibodies to CD20, R persists in the circulation for long-periods, rarely generates human anti-mouse antibodies and interacts with human effector cells including T-lymphocytes. The latter is though inhibition of antigen-presenting to the T-cells [15]. The beneficial effect of R is via suppression of antigen-presentation followed by inhibition of T-cell recruitment, blockage of the amplification pathway of IFN-alpha and finally its long-term effect by suppression B-memory cell expansion [16]. In the induction phase; a short-course of Corticosteroids was used to induce quick remission of IBP since the action of R takes at least 4 - 6 weeks [17]. In our patients; such dramatic effect was evident 6 weeks after R infusions and persisted for to 1 year (maintenance phase) while on R alone. Since, R efficacy is limited to 1 year; all patients were re-treated with yearly R-infusions. In our study; the efficacy of R was established, objectively, by improvement in TAS scores using BPDAI system [18] and decrease titers of its autoantibodies [19]. Finally, the small number of patients that were included in the study was due to its design as a tertiary medical clinic yet it provided support for a once/year therapy of a devastating disease.

5. Conclusion

R is a safe and effective treatment for IBP and such response further supports its immunopathogenesis.

Conflicts of Interest

The authors declare that they have no potential conflict of interest related to the contents of this article.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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