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Evaluation of rituximab infusion therapy in patients with recalcitrant pemphigus vulgaris

Akeel Hamed Jabur, Farah Saleh Abdul-reda*, Suhad Jassim abdlkadhim

Department of Medicine, College of Medicine, University of Al-Qadisiyah, Iraq

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ABSTRACT

The usual approach is to treat pemphigus vulgaris by corticosteroids and in some cases, immune suppressive agents may be indicated. The response is often satisfactory to the patient and acceptable clinically; however, the use of such agents is not free of side effects. Adverse effects associating the use of corticosteroids and immune-suppressing agents are numerous, but the principal side effects are those of fatal infections and neoplastic disorders. Therefore, we planned and conducted the current study to assess the efficacy of this drug in the treatment of recalcitrant cases of pemphigus vulgaris in a sample of Iraqi patients in the Mid-Euphrates region. To assess the efficacy of Rituximab in the treatment of recalcitrant cases of pemphigus vulgaris in a sample of Iraqi patients in the Mid-Euphrates region. The current cohort study included 10 patients with pemphigus vulgaris. Those patients were selected from the pool of patients visiting the dermatology consultation unit at Al-Diwaniyah teaching hospital, Al-Diwaniyah Province, Iraq during the period from January 2017 through June 2019. Age, gender, duration of disease, previous treatment, and maintenance treatment were the main variables included in the study; the outcome was a response to treatment classified as satisfactory, partially satisfactory and unsatisfactory. All patients were given an intravenous infusion of Rituximab in a dose of a 375 mg/m^2 in a weekly basis. The patients were followed for a minimum of 6 months. All patients were treated by intravenous rituximab and followed for a period of 6 up to 18 months, mean of 11.30 $\pm$3.83 months. Four (40.0 %) patients developed a satisfactory response, 5 (50.0 %) had partial satisfaction, and a single patient had an unsatisfactory response. Good rate of satisfaction can be obtained following the use of weekly based intravenous retuximab in patients with recalcitrant pemphigus vulgaris.

*Corresponding Author

Name: Farah Saleh Abdul-reda
Phone:
Email: Farahsalih753@yahoo.com

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INTRODUCTION

In dermatological practice, pemphigus is a medical term used to describe a number of disorders that are characterized by autoimmune damage targeting the stratified squamous epithelium of the skin and mucous membranes (Kasperkiewicz *et al.*, 2017; Cholera and Chainani-Wu, 2016). Principally there are three conditions: pemphigus foliaceus, pemphigus vulgaris and paraneoplastic pemphigus (Kasperkiewicz *et al.*, 2017). Other types also exist, including pemphigus vegetans, IgA pemphigus and pemphigus erythematosus (Tamgadge *et al.*, 2011). From a clinical perspective, these disorders are characterized by loss of cell adhesion (akan-

tholysis) leading to a manifestation of erosions and blisters (Furue and Kadono, 2017). Pemphigus vulgaris is usually a disorder of adults and is characterized initially by the involvement of oral mucosa in at least half of patients; however, during the disease course, the skin is often affected (Ohata *et al.*, 2014). The main clinical presentation is that of oral blisters that rapidly rupture, resulting in painful erosive lesions (Madala *et al.*, 2017; Shamran *et al.*, 2018). No oral mucosa is immune; nevertheless, the disease is predominantly seen in lips, buccal mucosa and soft palate mucosa (Cholera and Chainani-Wu, 2016; Chillab *et al.*, 2019).

Form epidemiologic point of view; the disorder is rare, with an estimated incidence of 1 to 5 per million annually (Tamgadge *et al.*, 2011; Santoro *et al.*, 2013). It can be seen in any ethnic group; however, Ashkenazi Jews rank the first in term of incidence. The disease is often seen during the 40s and 50s (Ariyawardana *et al.*, 2005; Abdulhussein and Al-Awsi, 2019).

It is an autoimmune disease that is characterized by the presence of autoantibodies, either circulating or tissue bound, that targets antigens of epithelial cell junctions, desmoglein 1 and desmoglein 3, leading to loss of cell adherence and formation of vesicles and blisters.

The usual approach is to treat pemphigus vulgaris by corticosteroids and in some cases immune suppressive agents may be indicated. The response is often satisfactory to the patient and acceptable clinically; however, the use of such agents is not free of side effects. Adverse effects associating the use of corticosteroids and immune-suppressing agents are numerous, but the principal side effects are those of fatal infections and neoplastic disorders. Therefore, the search for other forms of treatment modalities has been proven necessary, especially in resistant and recalcitrant forms of the disease (Graves *et al.*, 2007; Al-Grawi and Al-Awsi, 2018).

Rituximab is an efficient human/mouse chimeric anti-CD20 monoclonal antibody which acts by targeting B lymphocytes thereby reducing immunoglobulin production; however, it did not affect already present plasma cells, the main source of antibodies in human. A number of studies have evaluated the role of Rituximab in the treatment of pemphigus vulgaris (Zambruno and Borradori, 2008; Joly and Mouquet, 2007; Abdulhussein and Al-Awsi, 2019) however, results were conflicting. Therefore we planned and conducted the current study to assess the efficacy of this drug in the treatment of recalcitrant cases of pemphigus vulgaris in a sample of Iraqi patients in the Mid-Euphrates region.

MATERIALS AND METHODS

The current cohort study included 10 patients with pemphigus vulgaris. Those patients were selected from the pool of patients visiting the dermatology consultation unit at Al-Diwaniyah teaching hospital, Al-Diwaniyah Province, Iraq during the period from January 2017 through June 2019. Age, gender, duration of disease, previous treatment, and maintenance treatment were the main variables included in the study; the outcome was a response to treatment classified as satisfactory, partially satisfactory and unsatisfactory. All patients were given an intravenous infusion of Rituximab in a dose of a 375 mg/m^2 in a weekly basis. The patients were followed for a minimum of 6 months.

This current study was accepted by the institutional ethical approval committee, and verbal consent was obtained from any participant, after full illustration of the purpose and the procedure of the current study.

Obtained data were then transferred into an SPSS (version 23) spreadsheet. Numeric data were expressed as mean, range and standard deviation, whereas, categorical data were expressed as number and percentage. Willcoxon test was used to compare the mean number of lesions before and after treatment. The level of significance was set at $P \leq 0.05$.

RESULTS AND DISCUSSION

The current study included 10 Iraqi patients with pemphigus vulgaris, data about whom were collected during approximately one and a half year. The demographic characteristics of those patients are outlined in Table 1. Their ages have ranged from 32 up to 60 years with a mean age of 47.60 $\pm$8.09 years. The sample included 5 males and 5 females because of the rarity of the disease; the male to female ratio thus was 1:1. Disease duration has ranged from one to 10 years, with a mean of 3.60 $\pm$2.56 years. All patients were on oral steroids and azathioprine at time of enrollment into the current study, as shown in table 1.

All patients were treated by intravenous rituximab and followed for a period of 6 up to 18 months, mean of 11.30 $\pm$3.83 months. Response to treatment is shown in Table 2. Four (40.0 %) patients developed a satisfactory response, 5 (50.0 %) had partial satisfaction, and a single patient had an unsatisfactory response. Response to treatment was no significantly correlated to patients' age, gender or du-

ration of disease; however, there was a significant positive correlation between duration of treatment and response to it, Table 3.

Table 1: Demographic characteristics of patients with Pemphigus Vulgaris

Characteristic	Value
Number of cases	10
Age (years)	
Range	32 - 60
Mean ±SD	47.60 ±8.09
Gender	
Male, n (%)	5 (50 %)
Female, n (%)	5 (50 %)
Male : Female ratio	1:1
Duration of disease	
Range	1 - 10
Mean ±SD	3.60 ±2.56
Previous treatment	
Oral steroids, n (%)	10 (100.0 %)
Azathioprine, n (%)	10 (100.0 %)

n: number of cases; SD: standard deviation

Table 2: Response of patients with pemphigus vulgaris to intravenous infusion of retuximab

Response	n	%
Satisfactory	4	40
Partial satisfaction	5	50
Unsatisfactory	1	10

Table 3: Correlation between responses to treatment and demographic characteristics of patients with pemphigus vulgaris

Characteristic	r	p
Age	0.081	0.825
Gender	0.115	0.751
Duration of disease	- 0.445	0.198
Duration of follow up	0.819	0.004**

** Highly significant at ≤ P 0.01

Although the disease pemphigus vulgaris is rare, many patients may face severe complications because of the disease and fatality may be seen in untreated or improperly treated patients. The disease is often treated by using corticosteroids or immune suppressive agents which offer a reliable response in the majority of patients. Nevertheless, a number of patients develop resistant to treatment. In addition, a number of patients may undergo side effects because of immune suppression. Therefore, the search for a new treatment or at least an adjuvant treatment that reduce the dose of steroid therapy is mandatory aiming at improving treatment response, reducing the duration of treatment and eliminating debilitating side effects.

In the current study, the patients enrolled had a resistant form of pemphigus vulgaris. Thus, they were convinced to try another mode of treatment which has already been tested by a number of authors (Graves *et al.*, 2007; Chalap and Al-Awsi, 2019). The response, whether partial or complete, was seen in 90 % of patients, in addition, unwanted side effects were not seen despite the relatively long duration of treatment. However, a single patient had the unsatisfactory result, but he did not develop any serious complication or side effects attributed to retuximab.

Some authors reported a number of side effects associating the use of retuximab in dermatological practice. Side effects are mainly mild infusion-related, including fever, headaches, nausea, chills, rash and ruritus, often observed with initial treatment. Such adverse effects can be reduced, giving antipyretics and antihistamines before the infusion. Severe side effects are uncommon but can be fatal. Anaphylaxis, Stevens-Johnson syndrome, viral infections or bacterial sepsis of the nervous system have been observed (Al-Awsi *et al.*, 2019; Al-Grawi and Al-Awsi, 2018; Joly and Mouquet, 2007). Nevertheless, none of these adverse effects were observed in our study, therefore we believe that using retuximab in resistant pemphigus vulgaris can offer response rate, negligible side effects and reduces the need for large doses of corticosteroids and immune suppressive agents.

CONCLUSION

Good rate of satisfaction can be obtained following the use weekly based intravenous retuximab in patients with recalcitrant pemphigus vulgaris. The use of rituximab in resistant pemphigus vulgaris can offer response rate, negligible side effects and reduces the need for large doses of corticosteroids and immune suppressive agents.

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