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Research Article

Retrospective Analysis of a Single- Kuwaiti Center Clinical Experience Toward Development of Proper Controlling Treatment of 84 Pemphigus Patients with a Long-Term Follow-Up: Efficacy and Safety of the Multidrug Protocol Combining Intravenous Immunoglobulin with the Cytotoxic Immunosuppressor Drugs

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ABSTRACT

Pemphigus is the name of a group of autoimmune pathological entities characterized by the formation of intraepithelial blisters in the skin and/or mucosa. Pemphigus vulgaris (PV) and Pemphigus foliaceus (PF) are considered as classical forms. Rare, non-classical forms of Pemphigus include: Pemphigus herpetiformis, IgA pemphigus, Paraneoplastic pemphigus, IgG/IgA pemphigus.

Aim: Aim of our study is to explore the prognostic influence of clinical, immunological and therapeutic drugs on disease course and remission in different pemphigus variants in Kuwait and to establish a safe and effective multidrug protocol.

Plan of the study is to make a correlation between epidemiological factors, therapy used and clinical and immunological remission, as well as, follow up of comorbidities in our patients. 84 patients were evaluated, from 1st January 1990 to 31st December 2013.

IVIG is used as a third-line adjuvant treatment initially flanked by high-dose systemic corticosteroids and steroid-sparing immune-suppressants. Thus, this multidrug IVIG regimen made it possible to achieve a rapid control of the pemphigus symptoms, with progression to a stable disease remission, while maintenance an overall safety of treatment.

Keywords: Pemphigus vulgaris; Pemphigus foliaceus; Bullous disease

INTRODUCTION

Pemphigus is the name of a group of autoimmune pathological entities characterized by the formation of intraepithelial blisters in the skin and/or mucosa [1]. Autoantibodies are directed against desmogleins (DsGs) on the surface of keratinocytes, which results in loss of cellular adhesion, and formation of intraepidermal bullae, the triggering event leading to antibody formation is unknown.

Pemphigus vulgaris (PV) and Pemphigus foliaceus (PF) are considered as classical forms. Rare, non-classical forms of Pemphigus include: Pemphigus herpetiformis, IgA pemphigus, Paraneoplastic pemphigus, IgG/IgA pemphigus [2]. The overall incidence of pemphigus is estimated at 0.076 to 5 in 100,000 person per year [3]. The incidence of pemphigus vulgaris is higher in women (Male: Female=1: 1.1–2.25) [4].

PV is the most common variant of Pemphigus, usually begins with painful ulcerations on oral and other mucosa. The primary skin lesions of pemphigus vulgaris are flaccid, thin-walled, easily ruptured blisters that appear anywhere on the skin surface [4]. Histological studies of PV lesions usually demonstrate acantholysis in the supra-basilar part of the epidermis [1]. Without appropriate treatment, pemphigus vulgaris can be fatal because large areas of the skin lose epidermal barrier function, leading to loss of body fluids or secondary bacterial infection.

The primary lesions in PF are flaccid, superficial vesicles and bullae of the skin. These lesions some-times may not be seen on examination because of their fragile and subsequent transient

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nature. More often, only secondary lesions, such as shallow erosions, are seen [5]. There are no mucosal lesions, even with widespread disease. Intradermal acantholysis occurs in the granular layer [6].

The intraepithelial expression patterns of Dsg1and Dsg3 in skin and mucous membranes differ. Dsg1 is expressed throughout the epidermis, but more intensely in the superficial layers, while Dsg3 is expressed in the lower portion of the epidermis, primarily in the basal and supra-basal layers. In contrast, Dsg1 and Dsg3 are expressed throughout the squamous layer of the mucosa, but the former is expressed at a much lower level than the latter [7].

The diagnosis of the pemphigus group of diseases is based on clinical picture and history, histopathologic diagnosis, and direct and indirect immunofluorescence [8]. Direct immunofluorescence (DIF) demonstrates an intercellular deposition of IgG and C3 in a "chicken-wire" lattice pattern. For diagnosis of any pemphigus disease, sensitivity of DIF has been found to range from 80–95% [6]. The substrate for indirect immune-florescence (IIF) usually Monkey esophagus (for PV) and Normal Human Skin (for PF); if autoantibodies from the patient's serum are present and bound, the fluorescein conjugated IgG anti-serum will fluorescence under microscopy [4], seen as an intracellular staining. The test is reported as a titer.

ELISA is a quantitative method for measuring antibody levels and a useful test for the diagnosis of pemphigus. This method is more sensitive and specific than IIF. It is also superior to sophisticated immunoblotting techniques [5]. Enzyme linked immunosorbent assays (ELISA) is helpful in distinguishing the different subtypes of pemphigus (mainly PV from PF) [4]. Patients suffering from mucosal-dominant PV usually have antibodies directed against Dsg3 but not Dsg1, whereas mucocutaneous PV is characterized by both Dsg3 and Dsg1 autoantibodies [9]. In PF patients usually are detected antibodies against Dsg1, but not Dsg3 [9]. In general, ELISA antibody titers fluctuate in parallel with the disease activity with time in any particular patient, although the titers do not necessarily reflect the disease severity among different patients [10], it is useful for monitoring of disease activity [11], planning therapy, or predicting flares before the onset of clinical evidence [12,13].

SUBJECTS AND METHODS

Aim of our study

To explore the prognostic influence of clinical, immunological and therapeutic drugs on disease course and remission in different pemphigus variants in Kuwait, to establish a safe and effective multidrug protocol (including systemic steroids, intravenous immunoglobulin and other immune-suppressor drugs). Complete and partial remissions were evaluated according to the definitions proposed by the International Pemphigus Committee [14]. At time of our study this kind of research has not been done in Kuwait before.

Plan of the study

Evaluation of all diagnosed cases of pemphigus vulgaris and its variants through their registered files in our autoimmune bullous clinic. Our ABCD was established in 1990. Full detailed data were collected from the respective files including clinical evaluation, efficacy of systemic steroids and other adjuvant medications. Serology blood results were collected our immunology lab. Starting point was from 1st January 1990 to 31st December 2013.

Serum collection (immunology study)

Blood was separated with centrifuge for 5 minutes on 3000 RPM. IIF was done on Monkey Esophagus (NOVA Lite, Inova Diagnostics, CA USA), and titers were reported as 10, 100, 200, 400, and 800. Titers for Normal Human Skin were 10, and 100. Normal Human Skin was prepared by splitting with 0.1 M saline.

Patients' sera were stored on -40^{0}C until a necessary number of cases was collected for DSG ELISA. Desmoglein ELISA was done using commercial MESACUP kits (MBL, Sakea, Japan), with a cut of point of 30. Direct immunofluorescence was done using DAKO kit (DAKO, Denmark) on all patients available on presentation; for some patients, DIF was done during the course of therapy if patients developed flare or unusual skin lesions.

RESULTS

Characteristics of the studied patients

In the beginning of the study, total 95 patients were collected, but 11 patients were excluded due to lack of information or loss of their FU. Our cohort study included 84 patients of pemphigus variants who were diagnosed in our ABCD (Autoimmune Bullous Clinic Department) in As' ad Al-Hamad Dermatology Center in Kuwait. Patients include 48 (57.1%) males and 36 (42.8%) females. The mean age of pemphigus onset was 40.92 + 12.4 years, and the median age was 42 years. The mean length of follow up was 6.7 + 5.5 years, and the median was 5 years (Table 1).

Table 1: Characteristics of patients with pemphigus variants (n=84).

Studied Patients	Total	Male	Female
No.	84	48	36
Age at onset in years	33	33	33
Mean	40.92	40.92	40
SD	12.48	12.48	12.62
Min-Max	15-65	15.00-65.00	17.00-65.00
Median	42	42	39
Length of follow up in year			
Mean	6.71	5.55	8.18
SD	5.38	4.48	6.48
Min-Max	1.00-25.00	1.00-17.00	1.00-25.00
Median	5	5	7

Pemphigus variants in the study

The study includes 62 patient's pemphigus vulgaris)2 patient Oral pemphigus +60 patients skin and mucosal pemphigus (, 15 patients pemphigus foliaceus, 3 patients pemphigus vegetans, 2 patients pemphigus erythematosus (P.E) or Senear-Usher syndrome, and one patient paraneoplastic pemphigus and one patient IgA pemphigus.

Epidemiological factors

Ethnic groups comparison is one of the considerable epidemiological factors included in our study, we divided the studied patients regard their nationality into Arabs and others. Table 2 shows the distribution of different ethnic groups, there is Arabs group 70 patients total, and14 patients others.

Table 2: Ethnic groups included in the study.

Arabs			Others		
Nationality	n	%	Nationality	n	%
Kuwaiti	38	45.24	Indian	5	5.95

Egyptian	19	22.62	Bengali	2	2.38
Syrian	4	4.76	Filipino	2	2.38
Palestinian	3	3.57	Pakistani	2	2.38
Saudi	3	3.57	Iranian	1	1.19
Lebanese	2	2.38	Sri Lankan	1	1.19
Somalian	1	1.19	Turkish	1	1.19

Clinical and Immunological Remission

Table 3 illustrates clinical remissions in our patients during the follow up period. There are 34 (40.4%) male patient who went into clinical remission on treatment and 14 (16.66%) male patient maintained clinical remission off treatment, while there are 22 (26.19%) female patients went into clinical remission on treatment and 13 (15.4%) achieved clinical remission off treatment, and one male paraneoplastic pemphigus patient passed away due to his malignancy before achieving clinical remission. Regarding immunological Remission, there were 24 (28.5%) male patients achieved immunological Remission and other 23 (27.3%) male patients did not. While 21 (25%) female patients got immunological remission and 15 (17.8%) female patient did not get it.

The clinical remission in our patients was defined as a complete cessation of blistering of skin and/or mucosal erosions for at least 6 months [14].)we put a longer period for remission than R14). Immunological remission was defined as IIF of patients being very low or negative (IIF titer ≤ 1/19 for three repeated calibrations, IIF done every three months).

In Table 4, IIF were available for 82 patients, and it was found that a non-significant correlation between pemphigus variants and base line IIF in their sera (p value=0.183). In Table 5 shows a non-significant relation of pemphigus remission On/Off treatment with IIF baseline of patients, P value=0.097, although it near the significant value (0.1). Regarding the result of IIFy and clinical outcomes of studied pemphigus patients. In Table 6, showed a non- significant association between IIFy (IIF after a year) and remission of disease On/Off treatment, P value=0.328. In Table 7, Dsg1b titers (Dsg1 baseline) were available for 66 patients of the 84 patients pemphigus variants, the titer was divided into, I) negative (- ve): 0-29, weak positive (+ ve): 30-100 and strong positive (+ +ve): >100, it was found that non statistical significant association between remission of disease On/Off treatment (Disease activity) of studied pemphigus variants and the Dsg1b titers, as P value=0.620.

Table 8 shows the base line Dsg3b of pemphigus variants, it was available to the same previous 66 patients, it was found that no significant association between Dsg3b and disease remission on/off treatment, P value=0.850. Table 9 fortunately the DIF were available for all 84 patients and it significantly correlated with remission of pemphigus activity in our patients, as P value=0.001. Statistical analysis of initial steroid dose and number of pemphigus relapse is blotted in Table 10, showed a non-significant correlation in between, P value=0.451. Table 11, shows non -significant association between total cumulative steroid dose (T.C.S.D) and pemphigus variants as, P value=0.263. Total steroid consolidation dose given to our patients achieved remission were classified into low steroid dose which <5000 mg, Moderate steroid dose 5000: 10000, and high steroid dose >10000 mg. Table 12, shows non -significant Correlation between total steroid consolidation dose (T. Sc.D) and Pemphigus Variants as, P value=0.426. Table 13, shows non -significant association between IIFy and presence or absence of immunosuppressive drugs, P value=0.069.

Co-morbidity detection in studied pemphigus patient

There were 11 cases having Hyperlipidemia (13.10%) before treatment who increased to 15 (17.86%) after the treatment. There were 3 cases having Obesity (3.57%) before treatment who increased to 22 (26.19%) after the treatment in Tables 14 and 15. There were 13 cases who having either hypertension or diabetes mellitus (15.48%) before treatment which became 11 (13.10%) cases after the treatment. With regard to osteopenia and Cushing's disease were not present before treatment, but were detected 16 (19.05%) and 3 (3.57%) respectively after the treatment. Two cases (2.38%) had Gastritis before treatment who increased to 3 (3.57%) after the treatment. Concerning Osteoporosis, the number of cases remained the same before and after the treatment, 2 cases (2.38%) (Table 16). Other less presented comorbidities were detected, two cases for each of heart disease, osteoarthritis, malignancy, thyroiditis, hiatus hernia, ulcerative colitis, pulmonary TB, HCV, and Acne form eruptions. One case for each of cardiomyopathy, adenoma, epilepsy, cholecystitis, myopathy, tubular adenoma, vitiligo, psoriasis, retinopathy, and cataract.

Table 3: Studied Patients Clinical and Immunological Remission.

Studied Patients	Clinical remission				Immunological remission			
	ON/ treatment		OFF/ Treatment		Positive		Negative	
	n	%	n	%	n	%	n	%
Male	34	40.47	14	16.66	23	27.38	24	28.57
Female	22	26.19	13	15.4	15	17.85	21	25

Table 4: IIFb (IIF baseline) of studied pemphigus variants correlation with each type of pemphigus variants.

Pem. Variants	-ve IIFb			+ve IIFb		
	-ve	+ve	++ve	22	22	22
	n	%	n	%	n	%
P.V	5	7.8	17	26.9	40	64.5
P.F	4	26.7	5	33.3	6	40
P.E	0	0	2	100	0	0
P.VEGET	0	0	0	0	2	100
Paraneo.p	0	0	1	100	0	0
IgA P.	0	0	1	100	0	0
P value	0.183					

Abbreviations: IIFb: Baseline immunofluorescence; P.V: Pemphigus Vulgaris; P.F: Pemphigus Foliaceus; P.E: Pempfigus Erythematosus; P.VEG: Pemphigus Vegetans; Paraneo p: Paraneoplastic pemphigus; IgA P.=IgA pemphigus.

Table 5: Relation of pemphigus remission On/Off treatment and (IIF baseline) of patients.

Remission On/OFF treatment	-ve IIFb		+ve IIFb			
	-ve		+ve		++ve	
	n	%	n	%	n	%
Remission Off Treatment	5	17.9	11	39.3	12	42.9
Remission On Treatment	4	7.1	15	26.8	37	66.1
P. value	0.097					

Abbreviation: IIFb: baseline indirect immunofluorescence.

Table 6: IIFy (IIF after a year) of studied pemphigus group correlation with clinical Remission of Disease On/Off treatment.

Remission On/OFF treatment	-ve IIFy		+ve IIFy			
	-ve		+ve		++ve	
	n	%	n	%	n	%
Remission Off Treatment	20	71.4	4	14.3	4	14.3
Remission On Treatment	31	55.4	15	26.8	10	17.9
P. value	0.328					

Abbreviation: IIFy-indirect immunofluorescence after a year.

Table 7: Relation of studied pemphigus group DsG1b with Remission of Disease On/Off treatment (Disease activity).

Remission On/OFF treatment	-ve Dsg1b		+ve Dsg1b			
	-ve		+ve		++ve	
	n	%	n	%	n	%
Remission Off Treatment	20	44.4	9	20	16	35.6
Remission On Treatment	8	38.1	8	38.1	5	23.8
P. value	0.620					

Abbreviation: IIFy-indirect immunofluorescence after a year.

Table 8: Relation of studied pemphigus group Dsgb3 with Remission of Disease On/Off treatment (Disease activity).

Remission On/OFF treatment	-ve Dsgb3		+ve Dsgb3			
	-ve		+ve		++ve	
	n	%	n	%	n	%
Remission Off Treatment	11	23.4	8	17.0	28	59.6
Remission On Treatment	6	30.0	3	15.0	11	55.0
P. value	0.850					

Missing cases 17; Valid cases 67; No significant correlation between DsG3 titre and disease activity.

Table 9: Correlation of studied pemphigus group DIF with Remission of Disease On /Off treatment (Disease activity).

Remission On/OFF treatment	-ve DIF		+ve DIF	
	No.	%	No.	%
Remission Off Treatment	25	41.7	35	58.3
Remission On Treatment	20	83.3	4	16.7
P. value	0.001			

Table 10: Correlation between initial steroid dose and number of relapses of pemphigus activity (3pt on low dose steroid, 78pt on moderate steroid dose and 3 patients on high dose steroid. One patient had died and did not reach control stage).

No. of Relapses	Initial Steroid Dose					
	Low steroid dose		Moderate steroid dose		High steroid dose	
	n	%	n	%	n	%
No Relapses	0	0.0	24	30.8	2	66.7
1-3 Relapses	1	33.3	32	41.0	1	33.3
>3 Relapses	2	66.7	22	28.2	0	0
P. value	0.451					

Table 11: Relation between Total Cumulative Steroid Dose (T.C.S.D) and Pemphigus Variants.

Total Cumulative Steroid Dose	Pemphigus Variants													
	P.V		P.F		P.E		P.Veg		Para.P		LIGA.P		TOTAL	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Low dose	11	17.2	1	6.7	0	0	2	100	0	0	0	0	14	16.7
Moderate dose	16	25	7	46.7	1	100	0	0	1	100	1	100	26	31
High dose	36	56.3	7	46.7	0	0	0	0	0	0	0	0	43	51.2
P value	0.263													

Abbreviation: T.C.S.D: Total Cumulative Steroid Dose.

Table 12: Relation between Total Steroid Consolidation Dose (T. Sc .D) and Pemphigus Variants.

Total Steroid Dose (T. Sc .D)	Pemphigus Variants												TOTAL	
	P.V		P.F		P.E		P. Veg		Para. P		LIGA.P			
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Low dose	10	15.6	2	13.3	1	100	0	0	1	100	0	0	14	16.7
Moderate dose	31	48.4	9	60.0	0	0	1	50	0	0	1	100	42	50.0
High dose	23	35.9	4	26.7	0	0	1	50	0	0	0	0	28	33.3
P value	0.426													

Table 13: Relation between IIFy (IIF titre after a year) and Presence or Absence of immunosuppressive drugs.

Immunosuppressive Drugs (ISD)	-ve IIFy					
	-ve		+ve		++ve	
	N	%	N	%	N	%
Off ISD	2	22.2	3	11.5	1	2.0
On ISD	7	77.8	23	88.5	48	98.0
P. value	0.069					

Table 14: Relation between Clinical Remission On/Off Treatment and given or non-given IVIG.

IVIG Off/On	Remission Off TTT		Remission On TTT	
	n	%	n	%
Off IVIG	7	25.00%	25	44.60%
On IVIG	21	75.00%	31	55.40%
P value	0.081			

Table 15: Relation between TCSD (Total Cumulative Steroid Dose) and given or non- given IVIG.

IVIG Off/On	TCSD					
	low		moderate		high	
	n	%	n	%	n	%
Off IVIG	12	85.7	15	57.7	25	56.81
On IVIG	2	14.3	11	42.3	19	43.18
P value	0.127					

Table 16: Comparison of between different comorbidities before and after treatment.

Comorbidities	Before	After	0.127	0.127
	n	%	n	%
Hyperlipidemia	11	13.10	15	17.86
Obesity	3	3.57	22	26.19
Hypertension	13	15.48	11	13.10
Diabetes mellitus	13	15.48	11	13.10
Osteopenia	0	0.00	16	19.05
Gastritis	2	2.38	3	3.57
Osteoporosis	2	2.38	2	2.38
Cushing's disease	0	0.00	3	3.57

DISCUSSION

Pemphigus is a compendious word includes many subtypes of rare autoimmune bullous diseases that affect the skin and mucous membranes. This group includes pemphigus vulgaris, pemphigus foliaceus, pemphigus erythematosus, para-neoplastic pemphigus, pemphigus herpetiformis, and IgA pemphigus. Pemphigus has a chronic course leading to high morbidity and mortality therefore needs follow up on the long run, whereas treatment protocol has progressed over the last years [15]. Systemic steroids are still the main corner stone in pemphigus treatment, but we have now a therapeutic arsenal of new drugs that have been found to change the prognosis of autoimmune diseases including the autoimmune bullous dermatoses. There are insufficient and sometimes inconclusive observational studies examining the prognostic factors affecting the out-come of pemphigus patients, although some of these studies estimate mortality and co-morbidities associations among patients with pemphigus [16], but lacked demonstrating particular successful therapeutic modalities and the newly extended drugs interventions including IVIG. In our study we aim to present an efficient and complete follow up of our pemphigus patients thorough long run follow up which has reached 25 years in some patients Table 1. Pemphigus vulgaris incidence substantially vary around the world as it is considered the most common subtype of pemphigus variants [17], and this presented in our study, in which PV includes 62 (73.8%) patients from the 84 patients. In Table 3, pemphigus patients (66.66 %) have showed clinical remission on treatment, while 32.06% have showed clinical remission off treatment, so maintenance of pemphigus remission needs keeping on treatment with close clinical monitoring of efficacy and safety of treatment [18]. Total patients who achieved immunological remission were 53.57%, while 45.23% did not, regardless they were on or off maintenance treatment.

The positivity of initial autoantibodies IIFb for the studied patients was non- significant with the different pemphigus variants Table 4, another studies, IIF is positive in approximately 70–90% of pemphigus patients but lacks the ability to differentiate definitively between PV and PF since both have IgG antibodies directed against keratinocyte cell surface [19,20]. An universally lack of substrate sensitivity in IIF may be contributing factor, but monkey esophagus has been elucidated as the most sensitive screening test which used in our study. In Table 5 showed a non- significant relation between pemphigus remission On/Off treatment and IIFb of patients sera.

There is a controversy with regard to the value of IIF as a screening test, some previous studies considered it as useful marker of disease activity, although the titers do not necessarily reflect the disease severity among different patients.

In deed some patients who achieved clinical remission still had high immunological titers of IIF. In these patients the treatment should be continued until getting a negative or weak IIF, then the medications discontinued (Immunological remission result was considered after obtained two repeated consecutive IIF became negative three months apart) [21,22]. In Table 6 IIFy (IIF after a year) of studied pemphigus patients did not show any significant relation with clinical remission of disease on/Off treatment. A previous study concluded that IIF titers did not always correlate with the disease severity, and are not consistent enough to serve as a guide for therapy or for monitoring the disease activity [23,24] and subsequently this titer will not be the only judgmental factor for pemphigus management, which this goes with our results. Tables 7 and 8 shows a non- significant relation of DsGb1,3 ELISA studied pemphigus groups with remission of Disease On/Off treatment (Disease activity). Our results are controversy with other study that showed positivity of Dsgb1/3 with oral and skin disease reflects PV severity in addition ELISA titers measuring the Dsg1,3 have been found to consistently correlate with disease activity in PF throughout the patient's clinical course [25,26], but in our study the non -significant statics, might be explained, that the correlation was between DsGb1,3 ELISA and pemphigus groups not only PV, and the small numbers in each compared group. Direct immunofluorescence (DIF) of perilesional skin, is the gold standard in the diagnosis of pemphigus. Studies have observed that DIF performed during the periods of clinical remission is valuable in the management of the disease as a negative DIF may be viewed as a state of immunological remission [27]. In our study Table 9 shows a significant statistical correlation between studied pemphigus group and DIF at time of diagnosis with disease remission on/off treatment (Disease activity). Pemphigus patients with negative DIF at time of diagnosis showed clinical disease remission off treatment during follow up. Our result consistent with a previous study [28], many patients with negative DIF findings (73.3%) remained in clinical remission after discontinuation of treatment. In other side patients with positive DIF findings during remission had a relapse within 3 months after discontinuation of treatment [28]. Table 10, showed a non- significant correlation between the initial steroid dose and number of pemphigus relapses. Other study known that high dose prednisolone (>45 mg/day) treatment is associated to longer admission time in bullous pemphigoid patients, however no association between high/low corticosteroid dose and remission rate, relapse rate and treatment length was found, this study is compatible with our result [29]. Tables 11 and 12 shows a non-significant relation between neither the total cumulative steroid dose (T.C.S.D) and total steroid consolidation dose (T.Sc.D) consecutively in pemphigus variants. Regardless of pemphigus subtype, the formation of autoantibodies against desmosomal components has long been considered the chief event in the pathogenesis of pemphigus. In addition to the involvement of humoral immunity, the function of cellular immunity in it has been high- lighted [30]. The guidelines of both the EDF and BAD define systemic corticosteroids as the first-line treatment of PV and P.F are recommending initial treatment with predniso(lo)ne at a dose of 0.5–1.5 mg/kg/day (EDF) and 1.0 mg/kg/day (BAD) [31,32]. As showed in previous studies [30-32], there is no difference in systemic steroid dosage schedule for different non severe pemphigus subtype, accordingly; there is no a significant difference in T.C.S.D and T.Sc.D during long term therapy in pemphigus, this was also showen in our results.

Table 13 shows a non -significant association between IIFy and presence or absence of immunosuppressive drugs, later studies concluded that IIF titers did not always correlate with the disease severity, and are not consistent enough to serve as a guide for therapy or for monitoring the disease activity [33,34], and so even if immunosuppressive drugs have additional therapeutic effect, they will not reflected through IIFy titers during follow up of pemphigus patients, which explains our non -significant results.

In Tables 14 and 15 a non- significant association between clinical remission On/Off treatment and TCSD and however patients given or not given IVIG consecutively. IVIG is used as a third-line adjuvant treatment initially flanked by high-dose systemic corticosteroids and steroid-sparing immune-suppressants [35,36].

Thus, this multidrug IVIG regimen made it possible to achieve a rapid control of the pemphigus symptoms, with progression to a stable disease remission, while maintenance an overall safety of treatment [36].

CONCLUSION

The limitation of this study, was the patient's small number in each pemphigus variants, which made a limited use of statistics and resulted in a non- significant correlation in between different studied variant. It should be taken into consideration that this is a retrospective study; the associations are therefore not conclusive. The included experience in our study in management of pemphigus was not updated, as the end point was on 31st December 2013, but it was a long-term follow-up experience since 1990 toward a trial to get an established protocol for proper management for this serious, life threatening bullous disease.

CONFLICT OF INTEREST

There is no conflict of interest to be reported by any of the authors.

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