THINK GLOBALLY, ACT LOCALLY: EXPERT OPINIONS FROM ASIA ON THE DIAGNOSIS AND TREATMENT OF PEMPHIGUS VULGARIS

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ABSTRACT

BACKGROUND: *Pemphigus vulgaris (PV) is the most common blistering disease in Iran and many other Asian countries with a relatively high incidence and involvement of both skin and mucous membranes in majority of the patients.* ***AIMS:*** *To assess the opinions of Asian experts on the diagnosis and management of PV.* ***SETTINGS AND DESIGN:*** *It was a questionnaire-based mailed/e-mailed survey.* ***MATERIALS AND METHODS:*** *The questionnaire was sent to 29 dermatologists from different countries of Asia who treat autoimmune blistering disorders, with at least 5 years' experience in this field, and who visit at least five new PV patients annually. Questions included duration of experience, number of patients treated and diagnostic and treatment approaches for PV.* ***STATISTICAL ANALYSIS USED:*** *Percentage prevalence; some data are reported as mean ± SD.* ***RESULTS:*** *All of the 29 physicians participated in the survey; among them, 79.3% visit their patients within 6 months after the onset of symptoms. Diagnosis of PV is confirmed by histologic and direct immunofluorescence examinations by 65.5% of physicians. All of them initiate the treatment with corticosteroids (48.3% with a dose of at least 2 mg/kg/day prednisolone), and 89.7% add adjuvant immunosuppressors at the same time. Of the adjuvant agents used, azathioprine is used by 82.8% of physicians.* ***CONCLUSIONS:*** *Different trends in diagnostic techniques and treatment options for PV among the experienced authorities emphasize the urgent need for large-scale controlled trials in order to reach consensus standards in this field. In addition, regional and worldwide consensus meetings to consider all regional and genetic similarities and differences are highly recommended.*

Key words: *Corticosteroids, diagnosis, immunosuppressors, pemphigus, therapy*

Pemphigus is an autoimmune blistering disorder that affects skin and mucous membranes. Pemphigus vulgaris (PV) is the most common form, which may be fatal if left untreated.

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PV has a prevalence rate of 30 per 100,000 population[1] and an incidence rate of 1.0 per 100,000/year (0.67-1.6) in Iran,[1-4] which is much higher than many other countries-incidences varying from 0.076 in Finland[5] to 0.67 in Tunesia.[6] Only a population from Jerusalem[7] had an incidence of 1.6 per 100,000/year.

The mean age at onset of disease was between 38 and 42 years (pooled data from various studies: 41.35 ± 18.13 years),[1-4] which is similar to reports from other Middle East countries[7-9] and less than reports from Europe and U.S.A.[10-14]

The majority (70.4%)[1] of Iranian PV patients had both mucosal and skin involvement, with poorer prognosis and more treatment resistance.[1-4]

According to a study on MHC markers,[15] there is a possible common central Asian ancestral origin for non-Jewish Persian and Ashkenazi Jewish PV patients.

A wide variety of diagnostic and therapeutic approaches to PV, based on clinicians' experiences rather than solid evidence, exist. In this study, a survey was carried out to reveal the opinion of Asian expert dermatologists on diagnostic methods and management of PV.

MATERIALS AND METHODS

The study enrolled 29 dermatologists from different countries of Asia (23 from Iran and 6 from India, Kuwait, Turkey and Bangladesh) who are in charge of the treatment of autoimmune blistering disorders, with at least 5 years' experience in this field, and who visit at least five new PV patients annually. There was no discrimination and all potential candidates in Iran were invited and included. In addition, all potential Asian PV experts who had published at least one related paper with an available contact address were invited.

A questionnaire was mailed or e-mailed to study participants to assess their opinions about diagnostic and therapeutic approaches to PV. Information included duration of experience, number of patients treated annually and totally, number of new cases referred each year, diagnostic methods and treatment regimens.

The present study was approved by the Institutional Review Board of Center for Research and Training in Skin Diseases and Leprosy (CRTSDL), Tehran University of Medical Sciences.

Statistical analysis

SPSS version 11.5 for Windows software (SPSS Inc., Chicago, IL) was used to analyze the data. Some data are reported as mean ± SD.

RESULTS

Table 1 shows the answers given about different aspects of PV diagnostic approaches based on country (Iranian *vs.* non-Iranian) and compares these with a previous study.[16] In addition, Table 2 demonstrates the attitudes of surveyed experts towards the management of PV and compares these with a previous published study of Minouni *et al.*[16]

Participants' characteristics

Twenty-nine dermatologists responded and completed the questionnaires. They had a mean duration of experience of 17.4 ± 4.9 (range: 10 to 30) years in treating PV. Two physicians (6.9%) had treated less than 100

Table 1: Diagnostic considerations as reported by Asian pemphigus vulgaris experts and their comparison with a similar previous report, mainly from USA and Europe

		Iran (n=23)	*Other Asian countries (n=6)*	*Total Asian countries (n=29)*	*USA and Europe 15 (n=24)**
Duration of PV therapy, mean years		17.2	18.9	17.5	20
Total treated PV patients (%)	<100	4.3	16.7	6.9	Total of 2050 patients
	100-399	56.5	66.7	58.6	
	400-1000	34.9	16.7	31.0	
	>1000	4.3	0.0	3.4	
No. of new PV patients treated last year (%)	5-10	34.9	33.3	34.5	Total of 496 patients per year
	11-30	26.1	66.7	34.5	
	31-50	13.0	0.0	10.3	
	51-100	21.7	0.0	17.2	
	>100	4.3	0.0	3.4	
Referral delay (%)	3 months or less	17.4	50.0	24.1	50.0
	3 to 6 months	60.9	33.3	55.2	
	6 to 12 months	21.7	0.0	17.2	16.7
	More than a year	0.0	16.7	3.4	25.0
Gold standard of PV diagnosis (%)	Histology	13.0	16.7	13.8	0.0
	Histology + DIF	65.3	66.7	65.5	95.8
	Histology + DIF + IIF	21.7	16.7	20.7	0.0
	IIF	0.0	0.0	0.0	4.2

*Most data were reported as percentage due to uniformity of reporting, as in the study by Mimouni *et al.*[15]
PV - Pemphigus vulgaris, DIF - Direct immunofluorescence, IIF - Indirect immunofluorescence

patients, 17 (58.6%) had treated 100-399, 9 (31.0%) had treated 400-1,000 and 1 (3.4%) had treated more than 1,000 patients with PV during their lifetime. Ten dermatologists (34.5%) treat 5-10 new cases of PV each year, 10 (34.5%) treat 10-29, 3 (10.3%) treat 30-49, 5 (17.2%) treat 50-99 and 1 (3.4%) treats 100 or more new patients yearly.

Referral delay

Twenty-three (79.3%) clinicians reported that they see the patients within 6 months after the onset of symptoms; 5 (17.2%) physicians reported that they receive referrals between 6 months and 1 year; while 1 (3.4%) reported a lag time of more than 1 year from symptom onset to referral.

Diagnosis

Nineteen (65.5%) of the study participants establish the diagnosis of PV by histologic and direct immunofluorescence (DIF) studies; 6 (20.7%) consider histology, DIF and indirect immunofluorescence (IIF) to confirm their diagnosis. Four (13.8%) clinicians make diagnosis only on histologic evidence.

Therapy

Treatment protocol

All of the clinicians use corticosteroids initially in treatment of PV. Twenty-six (89.7%) clinicians initiate the therapy in conjunction with an adjuvant immunosuppressant, and two (8.7%) initiate with prednisolone alone. Among those who administer corticosteroids in combination with an adjuvant, three Indian experts (10.3%) prefer to prescribe dexamethasone-cyclophosphamide pulse,[17,18] and all others use prednisolone plus immunosuppressant.

Table 2: Therapeutic considerations as reported by Asian pemphigus vulgaris experts and their comparison with a similar previous report, mainly from USA and Europe

		Iran (n=23)	*Other Asian countries (n=6)*	*Total Asian countries (n=29)*	*USA and Europe 15 (n=24)**
Initial treatment protocol (%)	Prednisolone alone	8.7	16.7	10.3	45.8
	Prednisolone + steroid-sparing agent	91.3	50.0	82.8	16.7
	Dapsone or gold or tetracycline	0.0	16.7	3.4	20.1
	Dexamethasone-cyclophosphamide pulse	0.0	33.3	6.9	0.0
Initial dosage of prednisolone (%)	1 mg/kg/d	8.7	16.7	10.3	50.0
	1-1.5 mg/kg/d	13.0	33.3	17.2	31.0
	1.5-2 mg/kg/d	21.7	33.3	24.1	19.0
	≥ 2 mg/kg/d	56.5	16.7	48.3	
Final dosage of prednisolone in a controlled patient (%)	0 mg/d	69.6	66.7	69.0	37.0
	5 mg alternate daily	4.3	0.0	3.4	11.0
	5 mg/d	26.1	16.7	24.1	26.0
	10 mg/d	0.0	16.7	3.4	26.0
Choice of adjuvant therapy (%) azathioprine	91.3	50.0	82.8	44.0	
	Mycophenolate mofetil	0.0	0.0	0.0	20.0
	Cyclophosphamide	4.3	50.0	13.8	16.0
	Cyclosporine	4.3	0.0	3.4	4.0
	Mycophenolate mofetil and methotrexate	0.0	0.0	0.0	8.0
Maintenance duration for adjuvant agent (%)	6 to 12 months	39.1	33.3	37.9	46.0
	1 to 2 years	56.5	50.0	55.2	36.0
	> 2 years	4.3	16.7	6.9	18.0
Disease control definition (%)	Absence of new blisters	82.7	50.0	75.9	53.0
	Blister free skin	0.0	50.0	10.3	15.0
	Healing of most lesions and negative Nikolsky sign	4.3	0.0	3.4	0.0
	Healing of most lesions and absence of new blisters and negative Nikolsky sign	13.0	0.0	10.3	0.0
	Reduction in the number of blisters	0.0	0.0	0.0	32.0

*Most data were reported as percentage due to uniformity of reporting, as in the study by Mimouni *et al.*[15]

None of the participating experts currently uses other nonsteroidal agents (gold, tetracycline, dapsone) as the first choice in therapeutic regimen except one dermatologist, who sometimes considers dapsone as an initial therapy.

Initial prednisolone dosage

Three of them (10.3%) prescribe prednisolone at a dose of 1 mg/kg/day, 5 (17.2%) administer 1-1.5 mg/kg/day, 7 (24.1%) administer 1.5 up to 2 mg/kg/day and 13 (56.5%) administer at least 2 mg/kg/day at the time of diagnosis.

Preferred corticosteroids sparing immunosuppressors

Of all the adjuvant immunosuppressive agents, azathioprine is used by 24 (82.8%) of the physicians; cyclophosphamide is used by 4 (13.8%) and cyclosporine is prescribed by only 1 (3.4%) physician.

Tapering method

Considering the long-term strategy, 20 (69.0%) physicians reported that they set their goal to discontinue corticosteroid therapy completely, whereas 1 (3.4%) stated an alternate daily prednisolone dose of 5 mg as the ultimate goal and 7 (24.1%) had a goal of prescribing prednisolone at a dose of 5 mg daily. Eleven dermatologists (37.2%) keep on using the immunosuppressor for 6 months to 1 year, 16 (55.2%) maintain the regimen for 1 to 2 years and 2 (6.9%) continue immunosuppressive therapy for more than 2 years.

Disease control definition

Of the clinicians questioned, 22 (75.9%) defined disease control as the development of no new lesions and healing of most of the previous lesions; 1 (3.4%) defined it as vanishing of most of the lesions with negative Nikolsky's sign; 3 (10.3%) considered the control of disease as healing of majority of lesions, appearance of no new lesions, with negative Nikolsky's sign; and 3 (10.3%) define disease control as blister-free skin.

Corticosteroids *vs.* immunosuppressors

Following control of PV, 21 Iranian dermatologists (91.3%) stated that they reduce the immunosuppressor dose after the reduction in corticosteroid dose, whereas 2 Iranian (8.7%) clinicians reported that they initially decrease the dose of immunosuppressor.

DISCUSSION

Since the worthwhile advent of corticosteroids in 1950s, the fatal outcome and grave prognosis of PV have altered dramatically, albeit corticosteroid-induced morbidities.

In this study, the opinion of Asian (mostly west Asia) dermatologists with great experience in PV was obtained.

The differences between the present study and the study by Mimouni *et al.*[16] in terms of more rapid referral of PV patients to expert dermatologists could be rationalized by differences in disease severity at onset.

Clinical features of skin and mucosal lesions, demonstration of acanothlysis in biopsy specimens and demonstration of pemphigus autoantibodies in tissue, serum or both are the three main clues to confirmation of PV diagnosis.[19] In this study, it was found that about two-thirds of the physicians confirm their diagnosis by histologic and DIF examinations.

Considering the role of pemphigus autoantibodies in the pathogenesis of PV, it seems that a step-by-step treatment with moderate doses of corticosteroids in combination with immunosuppressors - to maximize efficacy and minimize the corticosteroid-related morbidities - is a safe and effective therapeutic approach.[16] We observed that all of the experts initiate the treatment of PV with corticosteroids, either alone or in conjunction with immunosuppressors. However, the study by Mimouni *et al.* revealed that 25% of physicians initially use nonsteroidal agents (gold, tetracycline, dapsone) or try to

eliminate potential triggers.[16] In the present study, only one expert prefers dapsone as an optional initial therapy in some circumstances.

Another important finding is that the majority of experts (82.8%) add adjuvant immunosuppressor to corticosteroid at the time of treatment initiation, contrary to 16.7% reported by Mimouni *et al.*[16] This fact can be simply explained by the severe nature of the disease in Asia.

Most of the participating physicians initiate prednisolone at a dose of more than 1.5 mg/kg/day (72.4%), whereas half of US/European dermatologists[16] initiate prednisolone therapy with 1 mg/kg/day. In one 20-year study, 782 out of 1,111 Iranian PV patients (70.4%) had both skin and mucous membrane involvement.[1] Hence, so many dermatologists in Iran and some other Asian countries prefer to start with higher doses of prednisolone, mostly in combination with an adjuvant drug from the beginning. The dosage is often reduced by 30% after clinical response in 10-14 days and then tapered by 10 mg/week until 30 mg and slower afterwards.[20] Even many experts who preferred treating PV with 1 mg/kg prednisolone increase the dosage in a stepwise manner in case of a lack of response after 5-7 days.[21,22]

Similar to other countries,[16] azathioprine is the most frequently prescribed immunosuppressive agent by Asians. This may be due to its lower cost, proven efficacy and acceptable safety profile even in combination with high doses of prednisolone.[23,24] Nausea and increased blood pressure are the most common adverse events for 2 mg/kg azathioprine plus 2 mg/kg prednisolone seen in a trial.[24] None of the Asian experts prefer to use Mycophenolate mofetil as an adjuvant primarily, which is contrary to US/European study.[16]

Moreover, we found that most of the experts (69.0%) consider the complete discontinuation of corticosteroids as their final goal of treatment. Paradoxically, only 37% of US/European experts[16] eliminate prednisolone after disease control.

A considerable proportion of physicians (75.9%) in this study defined disease control as the development of no new lesions and healing of most of the previous lesions, confirming previous findings with less controversial choices among Asians.

The main limitation of this study could be that we cannot completely generalize the attitudes of the whole continent. However, the study promotes so many controversies in expert opinions from different parts of the world (old world *vs.* new world), which can be explained in different fashions.

To sum up, a wide variety of diagnostic and therapeutic approaches to PV is apparent among the most experienced clinicians in this field. Therefore, large-scale randomized controlled trials would be essential to resolve existing controversies in the management of such potentially fatal disease and to achieve

a consensus among authorities on the matter.

In addition, as PV is widely variable in different parts of the world and in the absence of any published systematic reviews, regional and worldwide consensus meetings to implement all similarities and differences with respect to genetic background, degree of disease resistance and cultural concerns in different regions are highly recommended.

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