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Oral Acitretin Versus Oral Zinc Gluconate as a Comparative Cross-Over Therapeutic Study in Treatment of Behcet's Disease

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ABSTRACT— Behcet's disease is a systemic disorder where its etiopathogenesis is not well determined and commonest manifestations are muccocutaneous but can involve eye, cardiovascular and neurological systems. There are many modalities of therapy topical and systemic. Isotretinoin has been tried as an effective therapy of muccocutaneous manifestations. In present work is to try a new retinoid like acitretin which has longer half life than isotretinoin. To evaluate the effectiveness of oral acitretin versus oral zinc gluconate in the treatment and prophylaxis of BD as a new therapeutic model. This cross over controlled therapeutic study that conducted in the Department of Dermatology -Baghdad Teaching Hospital the period from August 2013-May 2014.Twenty patients who fulfilled criteria of BD are included in this work and the investigation were included ordinary and oral pathergy test. They were given acitretin 25 mg orally once daily for three months to be seen on the day fourteenth firstly and then monthly to be assessed depending on the clinical manifestation index for Behcets disease. After three months, acitretin was stopped and patients were given 25 mg elemental zinc gluconate twice daily for another three months. Twenty patients were treated, 12 males (60%), and 8 females (40%), with male to female ratio 1.5:1. All these patients completed the study and their ages ranged between 20-59 (37.3±12.3) years. Pathergy both ordinary and oral were also minimized by this therapy while C- reactive protein was not much effective by this therapy. Zinc gluconate had also the same therapeutic action against these manifestations. CMI before treatment ranged between 1 and 11 (5.65±1.98). After acitretin therapy the mean of CMI started to decline to reach 2.65 ±2.03 in first month of the therapy, with (p=0.00001) which was statistically high significant and continued high significant till the end of the third month. After cessation of acitretin and zinc gluconate started the mean continued to decrease to reach 2.05±2.52 at the end of the first month which was statistically high significant then; started to increase to reach 3.3 ±2.31 at the end of six month of the therapy but statistically remained highly significant. Both acitretin and zinc gluconate had statistically significant effect in reducing severity and frequency of oral ulcers, genital ulcers, skin and rheumatologic manifestations. Acitretin and oral zinc gluconte had an effective therapy in addition to its prophylactic action in treatment of muccocutaneous manifestations of Behcet,s disease. Also acitretin was statistically significant better than zinc gluconate.

KEYWORDS: Oral Zinc Gluconate

1. INTRODUCTION

Behçet,s disease (BD) is a chronic, relapsing, multisystem disorder characterized by mucocutaneous, ocular, vascular and central nervous system manifestations. The exact etiopathogenesis of Behçet's disease has not been clarified. However, many studies indicate that the disease may be triggered by environmental factors,

genetic factors, immunological factors and biochemical factors [1], [2].

Acitretin is a synthetic oral retinoid that has been used by dermatologists over the last two decades for a number of cutaneous diseases like psoriasis, lichen planus, Darier disease, hand eczema and Congenital ichthyoses [3], [4].

Zinc is an essential metal ion necessary for growth, metabolism and maintenance of cell function. Zinc deficiency in human's results in growth retardation, male hypogonadism, skin changes, poor appetite, mental lethargy [5], [6].

2. Materials and Methods

Twenty patients with full criteria of BD was included in this study, which carried out in multidiscipline BD clinic (Deparment of Dermatology and Venereology, Baghdad Teaching Hospital) during the period between Augest 2013 and June 2014.The questionnaire is displayed in the. Clinical examinations were performed stressing on the following points: size, site, and number of oral and genital ulcer. The pathergy test was done using gauge 20 needle. The patients were seen after 48 hours and the results were recorded accorded according to the Dilson s scale table 1.

Table 1: Show the level.

Negative (-)	Only erythema 2< mm
Suspected (+/-)	Only erythma<3mm Only papule 1-2+erythema 2mm
Positive (+)	1+ papule 2-3mm+erythema 3mm 2+papule 3mm+erythema 3mm 3+pustule 1-2mm+erythema 3mm 4+pustule 2mm+erythema 3 mm

Oral pathergy has been introduced by pricking the mucosa of the lower lip with gauge 20 blunt disposable needles. In Baghdad Teaching laboratories; Hb, WBC, PCV, ESR, GUE, CRP, lipid profile, HLA typing for HLAB5 and HLAB27 investigations were done. The diagnosis was done depending on the international study group criteria for the diagnosis of BD (International Study Group for Behcet,s disease, 2013).Patients who fulfilled with international study group criteria were included. While the patients with the following manifestations were excluded from this work: neurological involvement, cardiovascular involvement, pregnant and nursing mother and other systemic manifestations. Acitretin used in a dose 25 mg daily. Patients were instructed to use these capsules orally once daily after meal for three months. Then they were given zinc gluconate tablets 25 mg (50mg zinc gluconate=7.5 elemental zinc) which instructed to take it twice daily for another three months. For each BD patient, a clinical manifestations index which is the numerical sum of the clinical feature that was proved as a useful tool to measure the response to treatment in BD was calculated.

3. Results

Clinical manifestations index before treatment ranged between 1 and 11 a with mean ± SD of 5.65+_ 1.98. After acitretin therapy the mean of CMI started to decline to reach 2.65 ±2.03 in first month of the therapy with (p=0.00001) which was statistically high significant and continued high significant till the end of the third month with (p-value> 0.000001). After cessation of acitretin and zinc gluconate started the mean

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continued to decrease to reach 2.05±2.52 at the end of the first month with (p=<0.000001) which was statistically high significant then; started to increase to reach 3.3 ±2.31 at the end of six month of the therapy but statistically remained high significant (p-value=0.0007) table2 and figure 1.

Table 2: Results of samples

		Therapy						
		Acitretin				Zinc gluconate		
	Baseline	After 14 days	After one month	After two month	After three month	After four month	After five month	After six month
Mean	5.65	3.8	2.65	2.55	2.1	2.05	2.7	3.3
SD	1.98083	2.46235	2.0844	2.1392	2.1001	2.523	2.408	2.319
P-value		0.006	0.00001	0.00001	<0.00001	<0.00001	0.00007	0.0007
		S	HS	HS	HS	HS	HS	HS

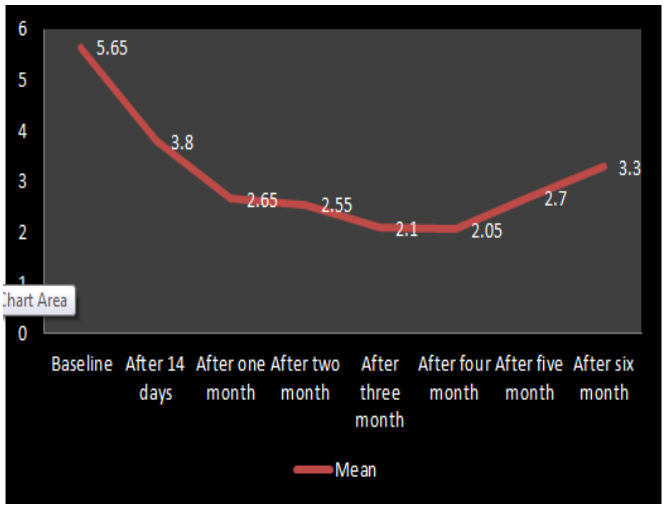

Fig.1: Curve of results

Both acitretin and zinc gluconate have statistically significant effect in reducing severity and frequency of oral ulcers, genitalulcers, skin and reumatological manifestations.

Pathergy test both ordinary and oral also minimized bythis therapy while C-reactive protein was not much effected by this therapy. Zincgluconate also had the same therapeutic action against these manifestations table 3 and figure2.

Table 3: Different between the positive and negative samples

Pathrgy test		Therapy						
		Acitretin				Zinc gluconate		
	Baseline	After 14 days	After one month	After two months	After three months	After four months	After five months	After six months
Positive	11 (55%)	10(50%)	5(25%)	4(20%)	2(10%)	3(15%)	5(25%)	9(45%)
Negative	9(45%)	10(50%)	15(75%)	16(80%)	18(90%)	17(85%)	15(75%)	11(55%
Total	20	20	20	20	20	20	20	20
P		0.95	0.15	0.07	0.009	0.02	0.15	0.81
Sig		NS	NS	NS	S	S	NS	NS

Oral pathergy test								
Positive	5(25%)	3(15%)	2(10%)	3(15%)	2(10%)	1(5%)	0(0%)	1(5%)
Negative	15(75%)	17(85%)	18(90%)	17(85%)	18(90%)	19(95%)	20(100%)	19(95%)
Total	20	20	20	20	20	20	20	20
P		0.73	0.45	0.73	0.45	0.20	0.05	0.20
Sig		NS	NS	NS	NS	NS	S	NS

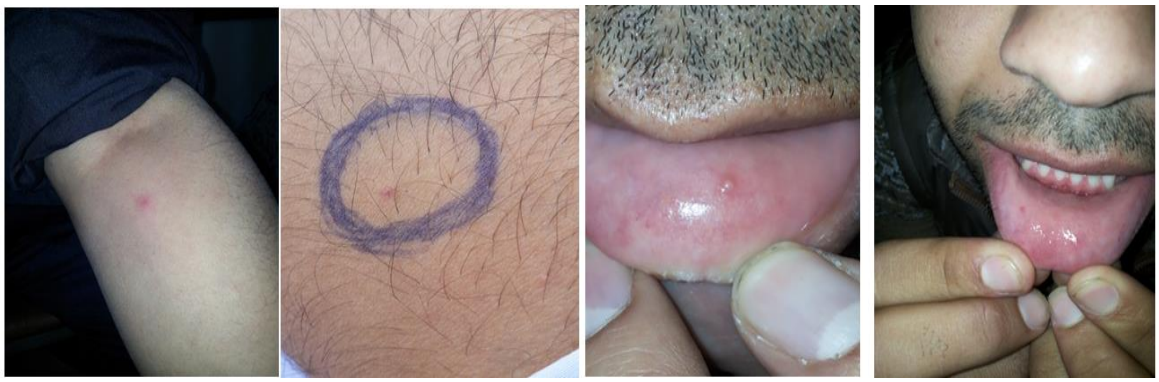

Fig.2: Positive pathegy test, Negative pathegy test, Positive oral pathergy test and Negative oral pathergy test.

4. Discussion

In the present work using oral acitretin showed a new effective therapy in controlling BD, as CMI was dramatically reduced after three months and the effect continued even one month after stopping the therapy. Accordingly acitretin has both therapeutic and prophylactic action [7]. Zinc gluconate was used in the next three months of Behcet,s therapy and also was effective at the end of the three months with statistically significant results. But when the two drugs were compared with each other acitretin was more effective than zinc glucconate with (p value<0.000001) at the end of three months and (P=0.00007) at the end of zinc gluconate therapy table 4 [8].

Table 4: Comparison between the effect of oral acitretin, oral isotretinoin and oral zinc sulfate on CMI in BD.

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		Therapy						
		Isotretinoin				Placebo		
Clinical manifestation	**Baseline**	**After 14 days**	**After one month**	**After two months**	**After three months**	**After four months**	**After five months**	**After six months**
Oral ulcers	22 (73.3%)	17 (56.6%)	20 (66.6%)	20 (66.6%)	16 (53.5%)	20 (66.6%)	23 (76.6%)	24 (80%)
p-value		0.09	0.23	0.23	0.048	0.23	0.432	0.147
significance		**NS**	**NS**	**NS**	**S**	**NS**	**NS**	**NS**
Genital ulcers	7 (23.3%)	5 (16.6. %)	3 (10%)	5 (16.6%)	4 (13.3%)	3 (10%)	3 (10%)	6 (20%)
p-value		0.102	0.046	0.10	0.048	0.046	0.046	0.245
significance		**NS**	**S**	**NS**	**S**	**S**	**S**	**NS**
Skin manifestations	19 (63.3%)	9 (30%)	4 (13.3%)	1 (3.33%)	1 (3.33%)	2 (66.6%)	4 (13.3%)	5 (16.6%)
p-value		0.02	0.0002	0.00003	0.0002	0.0002	0.001	0.02
significance		**HS**	**HS**	**HS**	**HS**	**HS**	**HS**	**HS**
Rheumatologic manifestations	26 (86.6%)	23 (76.6%)	22 (73.3%)	23 (76.6%)	24 (80%)	25 (83.3%)	25 (83.3%)	23 (76.6%)
p-value		0.103	0.136	0.103	0.147	0.154	0.154	0.154
significance		**NS**	**NS**	**NS**	**NS**	**NS**	**NS**	**NS**

Oral acitretin was statistically significant in reducing the number of oral ulcers with (p=0.002) at the end of three months as seen in present work. But when oral acitretin compared with oral isotretinoin there was no much difference in reduction rates. Genital ulcers were also highly reduced by oral acitretin with (p=0.02) at the end of three months but when compared with oral isotretinoin there was no much differerance in reduction rates [2]. Skin manifestations were statistically reduced by oral acitetin and similarly reduced by oral isotretinoin but the reduction rate in patients with acitretin was less than in isotretinoin. Rheumatological manifestations of BD like arthralgia and arthritis were significantly reduced by oral acitretin while these manifestations were slightly reduced by oral isotretinoin [3], [8].

Pathergy test was statistically reduced by oral acitretin which was very comparable to the effect of oral isotretinoin but the oral pathergy test was highly reduced by oral isotretinoin but not by oral acitretin. Oral acitretin had no effect on C-reactive protein in the present work while oral isotretinoin had statistically reduced C-reactive protein [9].

Oral zinc gluconate in the present work had a good therapeutic effect in reducing CMI with (p=0.0007) which was high significant but less effective when compared with oral zinc sulfate with (p-value<0.000001) which was also high significant [10].

5. Conclusions

Oral acitretin and oral zinc gluconate were a new effective thrapies in treatment of muccocutaneous manifestations of BD. Althoughacitretin was more effective than zinc gluconate. When oral acitretin compared with oral isotretinoin, acitretin was more effective in reducing CMI.Oral acitretin was less effective than oral isotretinoin in reducing the pathergy test including (ordinary and oral) and C –reactive protein.Acitretin, isotretinoin and zinc gluconate were less effective when compared with zinc sulfate in

reducing the CMI. Side effects were comparable between oral acitretin and oral isotretinoin, acitretin had more tendency to cause dryness of oral mucosa, conjunctiva and the skin. Oralacitrein has a good therapeutic impact in reheumatological manifestations and more effective than isotretinoin.

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