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Psychological and Neurological Impact of Oral Isotretinoin in Jordanian Subjects with Acne Vulgaris

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Abstract **Original Research Article**

***Background*:** Acne Vulgaris is the most frequent skin disease worldwide, reaching 70–87%. Isotretinoin a first class synthetic 13-*cis*-retinoid originated from Vitamin A is used for the management of Acne Vulgaris. The incidence of overall major depressive diseases worldwide is 13–16%. The incidence of psychological adverse effects in subjects managed using oral isotretinoin is 25.16%. ***Aim*:** To assess the psychological and neurological influence of oral isotretinoin in Jordanian subjects with Acne Vulgaris. ***Methods*:** Our retrospective investigation included 185 Jordanian subjects, of both sexes, aged 16-24 years, with severe nodulocystic Acne Vulgaris and on oral isotretinoin for (A) determination of: (1) intensity of Acne Vulgaris using the visual analog scale score (VAS-S: 0-100), (2) psychological impact using the Hamilton anxiety rating scale score (HAM-ARS-S:0-56) with the Montgomery Asberg depression rating scale score (MADRS-S:0-60) and (3) neurological adverse effects, all through baseline up to the fourth interview during a period of 4 months, one month apart and (B) screening for the need of antipsychotic medication after withdrawal of oral isotretinoin, at Prince Talal military hospital, JRMS, Mafraq, JORDAN, during the period Mar.2021-Aug.2023. ***Results*:** There was a remarkable enhancement in VAS-S through baseline up to the fourth interview (P<0.005). At first interview, the average VAS-S increased from 0 to 22.65. There was a remarkable increase in MADRS-S through baseline up to the fourth interview (P<0.005) with mild depression in 3 subjects (1.6%) and moderate depression in 1 subject (0.5%). There was a remarkable reduction in HAM-ARS-S during all interviews. (P<0.005). At the 3rd interview, 11 subjects (5.9%) were in the range of moderate anxiety and at the fourth interview, 4 subjects (2.2%) were in the range of severe anxiety. The most common neurological adverse effect was headache with most frequency at the fourth interview (135(72.97%)). ***Conclusion*:** Oral isotretinoin is safe and efficient in decreasing the intensity and disfiguration of Acne Vulgaris. Oral isotretinoin demonstrated an enhancement in anxiety but with a weak correlation with depression.

Keywords: Severe acne Vulgaris, Oral Isotretinoin: VAS-S; Psychology: MADRS-S, HAM-ARS-S, Neurology.

INTRODUCTION

Acne vulgaris is a long standing inflammatory with multiple causes disorder of the pilosebaceous unit of the face, neck, chest and back, following obstruction and inflammation of the pilosebaceous gland due to high sebum synthesis (androgen caused) and bacterial colonization (of hair follicles). It is the most frequent skin disease worldwide between adolescents and young adults (in both genders), reaching 70–87% [1]. Severe acne vulgaris (with nodules, cysts and scars) could induce cosmetic lesions and affect the quality of life causing anxiety and depression. For severe or resistant moderate acne, isotretinoin is the drug of choice.

Oral isotretinoin a first class synthetic 13-*cis*-retinoic acid originated from Vitamin A is used for the management of severe nodulocystic disfiguring Acne Vulgaris. Isotretinoin efficiently controls Acne Vulgaris by comedolytic, anti-inflammatory, decreasing of sebaceous gland activity and inhibitory action on proliferation of Propionibacterium acnes (anaerobic gram positive bacilli) [2], and normalization of follicular desquamation.

The incidence of overall major depressive diseases worldwide is 13–16% [1]. Systemic isotretinoin can cross the blood brain barrier because of its lipid solubility. Isotretinoin influences the hippocampus and prefrontal cortex in the brain which control mood and

coordinate cognition. Systemic isotretinoin has a risk of depression, aggression with psychosis (psychological) and neurological adverse effects. Efficient therapy could cause an enhancement in depressive features of subjects with acne. The incidence of depressive diseases during the administration of isotretinoin is between 1% and 11% [1]. The incidence of psychological adverse effects in subjects managed using oral isotretinoin is 25.16% [3].

The goal of our investigation was to assess the psychological and neurological impact of oral isotretinoin in Jordanian subjects with Acne Vulgaris.

METHODS

This retrospective investigation enrolled 185 Jordanian subjects, of both sexes, aged 16-24 years, with intense nodulocystic Acne Vulgaris and on oral isotretinoin for determination of intensity of Acne Vulgaris, psychological impact and neurological adverse effects, all through baseline up to the fourth interview, at Prince Talal military hospital, JRMS, Mafraq ,JORDAN, during the period Mar.2021-Aug.2023,after obtaining written informed consent from all participants or their guardians and approval from our local ethical and research board review committee of Jordanian Royal Medical Services. Subjects on immunosuppressant's, with chronic liver disease or pregnant were ruled out.

All participants were followed up for the appearance of adverse effects. Follow-up was performed during a period of four months, one month apart: baseline, first interview following one month, second interview following two months, third interview following three months and fourth interview following four months [1]. Symptomatic modifications in intensity of Acne Vulgaris were determined with VAS-S (0-100) [4], at every interview [2]. Psychological adverse effects were determined with Hamilton anxiety rating scale score (HAM-ARS-S: 0-56) with mild anxiety (if less than 17), moderate anxiety (18-24) and severe anxiety and with Montgomery Asberg depression rating scale score (MADRS-S: 0-60) with no depression (0-8), mild depression (9-17), moderate depression (18-34) and severe depression (35-60) [5], and [3], neurological adverse effects were recorded.

Statistics

Continuous parameters were evaluated using Wilcoxon pairs test and paired t-test. P value less than 0.05 was considered statistically remarkable.

RESULTS

105 subjects (56.8%) were men with an average age of 23.51 years and 80 subjects (43.2%) were women with an average age of 23.23 years. Most of subjects (74.6% (138)) were in the 19-22 years' age group. The average range of oral Isotretinoin dosage was 10-20 mg/day (0.2-0.5 mg/kg/day) Table I.

At baseline, VAS-S was 0 for all participants with no enhancement in Acne Vulgaris intensity. After that, there was a persistent and constant increase in VAS-S. At first interview, the average VAS-S increased to 22.65 with no subject demonstrating full enhancement regarding disorder intensity. There was persistent and constant enhancement in VAS-S through every interview with remarkable discrepancy to baseline score. Table II.

The most common neurological adverse effect was headache with the most frequency at the fourth interview (135(72.97%)) and with more in women (75%) than men (71.4%). Table III. The headache was increasing in incidence and intensity by time.

According to psychological impact, there was a remarkable discrepancy between the average baseline score (0.06) of MADRS-S and average score of every interview. The average score of MADRS during the first 2 interviews was under the minimum depression scale (0-8). At the third interview, 3 subjects experienced mild depression of MADRS-S (15.7) and 1 subject experienced moderate depression (18) at the fourth interview, when there was a need for medical therapy of antidepressant drugs beside the immediate isotretinoin withdrawal. Table IV.

There was a remarkable reduction in anxiety through the interviews. Table IV. Also we noticed a remarkable discrepancy between the average baseline score of HAM-A scale and the average score at each interview. The average score of HAM-A scale at the first 2 interviews was within the minimal range of anxiety scale (9-11, mild anxiety). At the 3rd interview, 11 out of 185 (5.9%) subjects were in the range of moderate anxiety (22) and they didn't need anxiolytic agents but just discontinuation of isotretinoin. At the fourth interview, 4 out 185 (2.2%) were in the range of severe anxiety and needed immediate anxiolytic agents.

Table I: Subjects demographics

Parameter	Description
No.	185
Age (yrs.) overall range Most common range	16-24 19-22
Gender (no.) M F	105 80
Isotretinoin dosage(range)mg/day	10-20

Table II: Visual analog scale score

Interviews (months)	VAS-S(average)	P
Baseline (0)	0	-
First (1)	22.65	<0.005
Second (2)	40.07	
Third (3)	66.53	
Fourth (4)	91.83	

Table III: Neurological adverse effects

	185				185	
interview	**First**	**Second**	**Third**	**Fourth**	**Men (105)**	**Women (80)**
Adverse effect						
Headache	58(31.4)	90(48.6)	120(64.9)	135(72.97)	75(71.4)	60(75)
Insomnia	0	2(1.08)	6(3.2)	15(8.1)	9(8.6)	6(7.5)

Table IV: Montgomery Asberg depression and Hamilton anxiety rating scale scores

Interview	MAD	P	HAM	P
Baseline	0.06	-	13.24	-
First	0.21	<0.05	10.87	<0.005
Second	0.47	<0.005	8.19	
Third	0.92		5.34	
Fourth	1.43		2.80	

DISCUSSION

Acne vulgaris is frequent following obstruction and inflammation of the pilo-sebaceous gland due to high sebum generation (androgen caused) and anaerobic bacterial establishment of hair follicles. Acne is the only indication for Isotretinoin. Isotretinoin acts as a prodrug and is transformed into all-trans-retinoic acid (ATRA) in the cytoplasm to be transported to the nucleus, where it binds to the nuclear retinoic acid receptor (RAR and RXR), isoforms a, b, and g. The known mechanisms of action are normalization of infundibular hyper keratinization, depression of the synthesis of cytokeratin's 1, 10 and 14, filaggrin and matrix metalloproteinase and increase of cytokeratin's 7, 13 and 19, laminin B1 and IL-1. Ugly skin lesions induced by acne vulgaris might induce anxiety and depression [6]. There was a remarkable reduction in average HAM-ARS-S in all interviews, which was similar to an investigation which showed a remarkable enhancement in anxiety in subjects on isotretinoin. The reduction in anxiety score was caused by the effect of isotretinoin on enhancement of disorder intensity [7]. There is no direct association between isotretinoin and depression by the fact that acne induces depression and anxiety. Managing acne with isotretinoin could control behavioral diseases [8-10].

There was a correlation between acne and socio-mental disturbance between adolescents [9]. There was no correlation between acne intensity and anxiety or depression [11]. Our investigation was similar to others where depression was found in a smaller group of acne subjects on isotretinoin [12]. There was a 1% frequency of depression between subjects with acne on isotretinoin [10]. There was a remarkable enhancement in symptomatic depression with oral isotretinoin [12]. Enhancement in depression is caused by character of life and acne enhancement more than enhancement in acne intensity [8]. Because isotretinoin crosses the blood-brain barrier, a biological mechanism between isotretinoin and depression is advocated. In the adult brain, receptors for retinoids are shown, and isotretinoin might control several neuronal genes. Serotonin (5-HT) is a neurotransmitter and a key mediator of mood. Imbalances in serotonin levels are related to low mood and depression. The effects of isotretinoin on the neurotransmitter's' serotonin (5-HT) and 5-HIAA (the main serotonin metabolite) in patients with acne vulgaris were determined. At the baseline, the average values were: 5-HT 10.66, 5-HIAA 74.77. Average values at 2-months of treatment were: 5-HT 9.64 (p = 0.633), 5-HIAA 44.31. At 4-months values modified to: 5-HT 13.07, 5-HIAA 32.83.

There was no remarkable relation between isotretinoin and modifications in the neurotransmitters 5-HT, 5-HIAA, or the ratio of the two. If the involving link is present between the two, it is likely mediated through a various neurochemical pathway [13]. Because isotretinoin could pass the blood-brain barrier, it may induce severe adverse effects but also it may reduce the psychological features of many psychological subjects.

Subjects with a family history of mental disorder were more liable to depression within therapy using isotretinoin [14]. In this investigation, there was no association with family history. Isotretinoin induced depression has multiple causes such as hypothalamic-pituitary-adrenal-axis hyperactivity induced by high retinoic acid, depression of biotinidase and disturbed

production of neurotransmitters caused by high homocysteine. Depressed subjects are liable to neurological adverse effects of isotretinoin as headache. In this investigation, all our participants in the symptomatic depression according to MADRS-S experienced intense headache as in other investigations [15]. Oral isotretinoin is persistently involved in major depression.

The analysis of 17 studies found a remarkable correlation between the administration of isotretinoin with enhanced features compared with the baseline before therapy. The data found no correlation between the administration of isotretinoin with the risk of depressive diseases. The investigation found a correlation between the administration of isotretinoin in subjects with acne with remarkably enhanced depression features [1]. Following three months of isotretinoin, 94.1%, 1.7%, 0.8% and 2.5% of subjects experienced normal mood, mild depression, moderate depression and severe depression, respectively. Following six months of isotretinoin, 95.8%, 0.8%, 0% and 1.7% of subjects experienced normal mood, mild depression, moderate depression and severe depression, respectively. Isotretinoin is fat-soluble and might easily pass the blood-brain barrier, influencing the central nervous system affecting the dopaminergic receptors, leading to depression and mood disturbances. There is a correlation between isotretinoin and depression, mostly in subjects that already have depression [16].

Although some investigations demonstrated good enhancement of anxiety and depression related to acne intensity itself, we found a remarkable increase of anxiety and depression scores of our patients related to the drug itself.

Psychological disorders that could exist in dermatological disorders may not require extra therapy and disappear with the therapy given for the dermatological disorder. So, therapy costs and unnecessary drug administration can be avoided. The intensity of the psychological disorder must be taken into account. Detailed history must be taken to decide if there is an old or new psychological disorder and the therapy started with the diagnosis, then the proper therapy must be chosen [17].

Our investigation has limitations. Azithromycin which was used for acne vulgaris might interfere with adverse effects and disorder intensity. Azithromycin was administered for 8 weeks and follow up was performed for 12 weeks. Gradual continuous increasing adverse effects after 8 weeks proves that the effect of Azithromycin was minimal. There was no control group for comparison.

CONCLUSION

Oral isotretinoin is efficient in decreasing the intensity of acne. Isotretinoin demonstrated enhancement in anxiety but depression was noted smaller group of subjects. Isotretinoin is safe.

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