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Effect of Systemic Isotretinoin Treatment on Depression and Other Psychological Symptoms: A Case-Control Study

Sistemik İzotretinoin Tedavisinin Depresyon ve Diğer Psikolojik Belirtiler Üzerine Etkisi: Bir Vaka Kontrol Çalışması

Türkan Tuğba YILDIZ[a], Mehmet MELİKOĞLU[b], Zeynep UTLU[a], Halil ÖZCAN[c]

[a]Department of Dermatology and Venereology, University of Health Sciences Erzurum City Hospital, Erzurum, Türkiye
[b]Department of Dermatology, Atatürk University Faculty of Medicine, Erzurum, Türkiye
[c]Department of Psychiatry, Atatürk University Faculty of Medicine, Erzurum, Türkiye

ABSTRACT Objective: Isotretinoin is highly preferred in the treatment of severe and resistant acne, but there are still disagreements about whether it has psychogenic side effects. In this study; we aim to investigate the changes in psychological symptoms before and after the treatment in a group of patients treated with isotretinoin. **Material and Methods:** A total of 110 patients who had moderate or severe acne, and decided to start isotretinoin treatment, were included. Acne Quality of Life Scale, Beck Depression Inventory (BDI), Beck Suicidal Ideation Scale, and Symptom Check List (SCL-90-R) Psychological Symptom Screening tests were performed and compared before starting treatment and at the 6th month of treatment. **Results:** In our study, in both the pre-treatment and post-treatment groups, the rate of patients at risk for depression was significantly higher in the group that had severe acne ($p<0.05$). The scores of psychiatric tests with moderate acne were found to be significantly lower than those with severe acne in all parameters ($p<0.05$). We have found that somatization, depression, phobic thoughts, and general symptom index scores were significantly higher in women before and after the treatment ($p<0.05$). Acne treatment was associated with improved quality of life and BDI scores in both male and female patients ($p=0.001$). SCL-90-R somatization, obsession, depression, sensitivity, anger, and general symptom index scores decreased significantly after the treatment. **Conclusion:** Our study objectively demonstrated that isotretinoin treatment does not cause depression and psychological symptoms, and even improves depression and psychological symptoms caused by acne and improves the quality of life.

Keywords: Acne; isotretinon; depression

ÖZET Amaç: İzotretinoin, şiddetli ve dirençli akne tedavisinde oldukça fazla tercih edilmekle birlikte psikojenik yan etkilerinin olup olmadığı konusunda hâlen görüş ayrılıkları bulunmaktadır. Bu çalışmada; izotretinoin ile tedavi edilen bir grup hastada tedavi öncesi ve sonrası psikolojik belirtilerdeki değişiklikleri araştırmayı amaçladık. **Gereç ve Yöntemler:** Çalışmaya orta veya şiddetli aknesi olan ve izotretinoin tedavisine başlamaya karar veren toplam 110 hasta dâhil edildi. Akne Yaşam Kalitesi Ölçeği, Beck Depresyon Envanteri [Beck Depression Inventory (BDI)], Beck İntihar Düşüncesi Ölçeği ve Belirti Tarama Listesi [Symptom Check List (SCL-90-R)] Psikolojik Belirti Tarama testleri tedaviye başlamadan önce ve tedavinin 6. ayında karşılaştırıldı. **Bulgular:** Çalışmamızda hem tedavi öncesi hem de tedavi sonrası gruplarda şiddetli aknesi olan grupta depresyon riski taşıyan hasta oranı anlamlı olarak daha yüksekti ($p<0,05$). Orta derecede aknesi olan hastalarda psikiyatrik test puanları şiddetli aknesi olanlara göre anlamlı olarak düşük bulundu ($p<0,05$). Kadınlarda somatizasyon, depresyon, fobik düşünceler ve genel semptom indeksi puanlarının tedavi öncesi ve sonrası anlamlı olarak yüksek olduğunu bulduk ($p<0,05$). Akne tedavisi, hem erkek hem de kadın hastalarda yaşam kalitesi ve BDI skorlarında iyileşme ile ilişkilendirildi ($p=0,001$). SCL-90-R somatizasyon, obsesyon, depresyon, duyarlılık, öfke ve genel semptom indeks puanları tedavi sonrasında anlamlı olarak azaldı. **Sonuç:** Çalışmamız, izotretinoin tedavisinin depresyon ve psikolojik belirtilere neden olmadığını, hatta akneye bağlı gelişen depresyon ve psikolojik belirtileri düzelttiğini ve yaşam kalitesini iyileştirdiğini objektif olarak göstermiştir.

Anahtar Kelimeler: Akne; izotretinoin; depresyon

Acne vulgaris is a chronic multifactorial inflammatory disease of the skin mainly seen in adolescence and progresses with inflammation of the pilosebaceous unit.[1] It is a very common disease and affects 70% to 87% of the population.[2] Treatment varies depending on the severity and morphology of acne. Topical treatments, especially topical retinoids, are preferred for mildly severe cases, and systemic regimens that include antibiotics, hormonal treatment, and oral retinoids are used in moderate and severe cases.[3]

Correspondence: Mehmet MELİKOĞLU
Department of Dermatology, Atatürk University Faculty of Medicine, Erzurum, Türkiye
E-mail: mmelikoglu@atauni.edu.tr

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Although isotretinoin has a strong effect, which makes it the first choice in the treatment of severe and refractory acne, it is a vitamin A analog and has some side effects and complications such as teratogenicity, liver dysfunction, and negative psychological effects.[4]

It was reported in previous studies that acne might cause mood disorders, including depression, and reduce the quality of life, like many chronic diseases. Acne vulgaris was associated with social and psychological disorders such as low self-esteem, depression, social phobia, anxiety, and suicidal thoughts.[5-7] Considering previous studies, although severe acne has more negative impacts on mood than chronic cutaneous disorders such as psoriasis or alopecia, the relation and aggravating role of isotretinoin with mood disorders is still controversial.[8,9]

Although some previous studies showed the negative effects of isotretinoin such as depression, it was also reported that there is no relation between isotretinoin and depression in recent meta-analyses, and even acne treatment improves depressive symptoms.[10] In some studies, it was argued that patients may have depression and suicidal ideas, but this is not drug-related and is related to the stress caused by acne on the patient. As proof of this, it was shown that the depression status of the patients improved with isotretinoin treatment. Consensus on these issues has not been reached yet, and it is recommended that isotretinoin not be used in patients who have suicidal ideas and that those with depression must be followed closely during the treatment process.[11]

In the present study, the purpose was to investigate the changes in psychological symptoms such as depression, psychological symptoms, quality of life, suicide, and suicidal ideas before and after the treatment in a group of patients treated with isotretinoin.

MATERIAL AND METHODS

A total of 110 patients who had moderate or severe acne, who agreed to participate in the study between April and October 2016 and decided to start isotretinoin treatment, were included in the study, which was conducted in Atatürk University, Faculty of Medicine, Department of Dermatology and Venereal Diseases. Patients with pregnancy, lactation, hyperlipidemia, history of atherosclerotic heart disease, liver dysfunction, use of drugs that interacted with isotretinoin (i.e. vitamin A, tetracycline, acitretin, carbamazepine, etretinate, minocycline, dexamethasone) were not included in the study. Patients with a previous history of psychiatric illness or those who used medication for a psychiatric illness were also excluded from the study. Isotretinoin treatment was started for those with normal liver function test results and normal lipid profiles. Care was taken to ensure that the beta human chorionic gonadotropin test result was negative in female patients. Acne severity was graded in 2002 according to the "Food and Drug Administration" 5-stage global system of acne grading.

The sociodemographic characteristics (i.e. age, gender, marital status, educational status, smoking, and acne severity) of the patients were recorded before the treatment. The patients filled in the Acne Quality of Life Scale (AQOLS), Beck Depression Inventory (BDI), Beck Scale for Suicide Ideation, and Symptom Check List (SCL-90-R) Psychological Symptom Screening test before starting the treatment and at the 6th month of the treatment.

Patients were divided into two groups as high and low risk for each area in the SCL-90-R scale. Patients with a score above 1 were considered high risk, and those with a score lower than 1 were considered low risk.

Patients were divided into two groups on the BDI. Those who scored 10 or higher were considered risky, and those below 10 were considered normal.

Isotretinoin treatment was started for the patients at a dose of 0.5 mg/kg/day in two divided doses for the first month. In the ongoing months, the dose was increased to 0.75-1 mg/kg/day, and the treatment was continued. Only oral isotretinoin was given to the patients as systemic treatment. Topical treatments were added to the treatment in some patients.

The SPSS 13.0 (SPSS Inc.,USA) program was used for the statistical analysis of the study data. Whether the data fit the normal distribution was checked with a histogram and tested with Kol-

mogorov-Smirnov. The t-test was used in dependent groups and independent groups for the data that had a normal distribution. The data that did not fit the normal distribution were analyzed with the Wilcoxon, Mann-Whitney U-test, Spearman's correlation test, and Kruskal-Wallis test. The chi-square test was used in independent groups and McNemar test was used independent groups for the categorical data. The confidence interval was taken as 95% and a p value of <0.05 was considered significant.

Ethical approval was obtained from the Local Ethics Committee of Atatürk University, Faculty of Medicine Clinic Research Ethical Committee (date: April 28, 2016, no: B.30.2ATA.0.01.00/). An informed consent form was obtained from all participants. The study was performed as per the latest version of the "Helsinki Declaration" and the "Guidelines for Good Clinical Practice".

RESULTS

A total of 110 patients were included in this prospective study (80 females and 30 males; 72.7% vs. 27.3%). The mean age of the patients was 21.78 (18-37 years). Having 74.5% (n=82) patients with undergraduate and graduate education levels increased the chance of data consistency. The mean body mass index was 22.3 (16.1-27). The demographic characteristics of the patients according to gender are given in Table 1.

TABLE 1: Descriptive statistics of the patient group.

	Male	Female	Total
Gender	30 (27.3%)	80 (72.7%)	110 (100%)
Education level			
Primary school	0 (0%)	3 (2.7%)	3 (2.7%)
High school	6 (5.5%)	16 (14.5%)	22 (20%)
University	22 (20%)	60 (54.5%)	82 (74.5%)
Master	2 (1.8%)	1 (0.9%)	3 (2.7%)
Smoking			
Not using	14 (12.7%)	73 (66.4%)	87 (79.1%)
1-10 pieces per day	9 (8.2%)	6 (5.5%)	15 (13.7%)
11-20 pieces per day	4 (3.6%)	0 (0%)	4 (3.6%)
More than 20 a day	2 (1.8%)	0 (0%)	2 (1.8%)
Social drinker	1 (0.9%)	1 (0.9%)	2 (1.8%)
BMI	23.3 (SD: 1.8)	21.9 (SD: 2.3)	22.3 (SD: 2.2)
Age	21.7 (SD: 2.5)	21.8 (SD: 3.2)	21.7 (SD: 3.0)
Acne severity			
Middle	22 (20%)	63 (57.3%)	85 (77.3%)
Severe	8 (7.3%)	17 (15.5%)	25 (22.7%)

BMI: Body mass index; SD: Standard deviation.

The psychological test scores of the patients before and after the treatment, including depression and quality of life scores, are shown in Table 2. Acne treatment was associated with improved quality of life and BDI scores in both male and female patients (p=0.001). Pre-treatment AQOLS mean was 16.01, standard deviation (SD): 5.14, post-treatment mean was 10.11, SD: 1.25, BDI mean pre-treatment 10.05, SD: 7.76, and post-treatment mean score was 6.55, SD: 4.72 (p<0.001).

TABLE 2: Comparison of psychiatric tests before and after treatment.

	Mean score before treatment	Mean score after treatment	p value
Acne Quality Life Index	**16.01 (SD: 5.14)**	**10.11 (SD: 1.25)**	***p <0.001**
Beck Depression Scale	**10.05 (SD: 7.76)**	**6.55 (SD: 4.72)**	***p<0.001**
Somatization	**0.80 (SD: 0.58)**	**0.79 (SD: 0.57)**	***p<0.05**
Anxiety	0.54 (SD: 0.55)	0.54 (SD: 0.55)	p>0.05
Obsession	**1.02 (SD: 0.71)**	**0.99 (SD: 0.69)**	***p<0.001**
Depression	**0.68 (SD: 0.60)**	**0.63 (SD: 0.54)**	***p<0.001**
Sensitivity	**0.94 (SD: 0.73)**	**0.89 (SD: 0.72)**	***p<0.001**
Psychotic symptoms	0.43 (SD: 0.51)	0.43 (SD: 0.50)	p>0.05
Paranoid thought	0.82 (SD: 0.72)	0.82 (SD: 0.73)	p>0.05
Anger	**0.59 (SD: 0.59)**	**0.56 (SD: 0.58)**	***p<0.05**
Phobic thought	0.39 (SD: 0.48)	0.38 (SD: 0.47)	p>0.05
General symptom index	**0.70 (SD: 0.49)**	**0.67 (SD: 0.48)**	***p<0.001**

SD: Standard deviation. * p<0.05

SCL-90-R somatization, obsession, depression, sensitivity, anger, and general symptom index scores decreased significantly after the treatment, but no significant differences were detected in the mean scores of anxiety, psychotic symptoms, paranoid thoughts, and phobic thoughts before and after the treatment. Somatization, depression, phobic thoughts, and general symptom index scores were significantly higher in women before and after the treatment ($p<0.05$). No significant differences were detected between men and women in other parameters ($p>0.05$). The values are given in detail in Table 3.

In the present study, none of the patients had suicidal ideations at the beginning of the treatment. No suicidal ideations developed in any of the patients after 6 months of isotretinoin treatment and no analysis was performed for the suicide scale.

TABLE 3: Comparison of psychiatric test scores by gender.

	Woman	Man	p value
Acne Quality Life Index			
Before treatment	15.8 (SD: 5.4)	16.4 (SD: 4.1)	p>0.05
After treatment	9.9 (SD: 1.0)	10.4 (SD: 1.7)	p>0.05
Beck Depression Scale			
Before treatment	10.2 (SD: 7.6)	9.6 (SD: 8.2)	p>0.05
After treatment	6.4 (SD: 4.4)	6.8 (SD: 5.5)	p>0.05
Somatization			
Before treatment	**0.91 (SD: 0.58)**	**0.51 (SD: 0.49)**	***p<0.05**
After treatment	**0.91 (SD: 0.57)**	**0.48 (SD: 0.46)**	***p<0.001**
Anxiety			
Before treatment	0.60 (SD: 0.57)	0.40 (SD: 0.47)	p>0.05
After treatment	0.59 (SD: 0.57)	0.40 (SD: 0.45)	p>0.05
Obsession			
Before treatment	1.07 (SD: 0.71)	0.88 (SD: 0.70)	p>0.05
After treatment	1.04 (SD: 0.70)	0.86 (SD: 0.68)	p>0.05
Depression			
Before treatment	**0.74 (SD: 0.60)**	**0.51 (SD: 0.57)**	***p<0.05**
After treatment	**0.69 (SD: 0.57)**	**0.48 (SD: 0.46)**	***p<0.05**
Sensitivity			
Before treatment	0.98 (SD: 0.72)	0.83 (SD: 0.77)	p>0.05
After treatment	0.92 (SD: 0.71)	0.81 (SD: 0.74)	p>0.05
Psychotic symptoms			
Before treatment	0.47 (SD: 0.53)	0.35 (SD: 0.47)	p>0.05
After treatment	0.46 (SD: 0.51)	0.35 (SD: 0.46)	p>0.05
Paranoid thought			
Before treatment	0.87 (SD: 0.75)	0.70 (SD: 0.65)	p>0.05
After treatment	0.86 (SD: 0.75)	0.71 (SD: 0.67)	p>0.05
Anger			
Before treatment	0.57 (SD: 0.57)	0.63 (SD: 0.66)	p>0.05
After treatment	0.55 (SD: 0.55)	0.62 (SD: 0.65)	p>0.05
Phobic thought			
Before treatment	0.44 (SD: 0.50)	0.25 (SD: 0.38)	*p<0.05
After treatment	0.43 (SD: 0.49)	0.25 (SD: 0.38)	*p<0.05
General symptom index			
Before treatment	0.75 (SD: 0.50)	0.56 (SD: 0.46)	*p<0.05
After treatment	0.71 (SD: 0.48)	0.55 (SD: 0.44)	*p<0.05

SD: Standard deviation. * p<0.05

When the relationship between the severity of acne and the psychiatric test scores of the patients was analyzed, the scores of those with moderate acne were found to be significantly lower than those with severe acne in all parameters ($p<0.05$). The severity of acne and the risk status in the SCL-90-R scale are examined. In the patient group with severe acne, high-risk patients were found to be significantly higher in all parameters except somatization compared to the patient group with moderate acne ($p<0.05$). When the risk change in the SCL-90-R scale was analyzed before and after treatment; although some patients transitioned from the high-risk group to the low-risk group after treatment, no significant difference was found in any of the parameters ($p>0.05$). Similarly, no significant correlation was found between gender and being a low or risky group in any of the parameters ($p>0.05$).

The effects of acne severity and isotretinoin treatment on BDI were examined. The risk of depression was significantly higher in patients with severe acne in both pre-and post-treatment groups compared to patients with moderate acne ($p<0.05$) (before the treatment, moderate acne: 70.6% normal, 29.4% risky. Severe acne: 44% normal, 56% risky) (after the treatment, moderate acne: 87.1% normal, 12.9% risky. Severe acne: 68% normal, 32% risky). It was found that there was a significant transition from the risky group to the normal group after the treatment ($p<0.05$). Before the treatment, 64.5% (n=71) was normal and 33.5% (n=39) was risky. After the treatment, 82.7% (n=91) was normal and 17.3% (n=19) was risky.

No significant relations were detected between gender and being a normal or risky group in the BDI ($p>0.05$).

DISCUSSION

Acne, which is a young adult disease and one of the most common causes of dermatology clinic visits, reduces the quality of life by causing psychiatric disorders such as depression, anxiety, low self-esteem, and social phobia.[4]

These negative psychological effects are more significant in female patients and patients with facial involvement. Kellett and Gawkrodger reported that acne caused more psychological problems in female patients, and Aktan et al. reported that anxiety levels were higher in females than in males.[12,13] The fact that the SCL-90-R somatization, depression, phobic thoughts, and general symptom index scores were higher in female patients than in males in our study explains the female dominance (72.7%) in the study.

Yüksel Başak and Ergin found that there were no significant differences in terms of gender, age, and quality of life.[14] In Table 3, it is seen that there were no relations between the psychiatric symptoms of the patients and age, marital status, and educational status ($p>0.05$), but the SCL-90-R somatization, depression, phobic thoughts, and general symptom index scores were higher in female patients than in males.

Many studies showed that with effective acne treatment, symptoms of anxiety and depression can be reduced and quality of life can be improved.[4,12,15,16]

Similarly, our data showed that AQOLS increased significantly after the acne treatment. The relationship between isotretinoin and depression is still a controversial issue although studies are reporting a relationship.[17]

There are also studies arguing that there is no increase in depression, suicide attempts, and other psychiatric diseases and that they even have curative effects on mood.[18-21]

In some studies reporting that it is associated with psychiatric disorders, it was argued that this fat-soluble drug crosses the blood-brain barrier affecting various parts of the central nervous system, including dopaminergic receptors, and causing depression and mood abnormalities.[22,23]

When the controlled studies that argued the contrary were examined, Marqueling et al. examined a total of 9 studies, 6 prospective and 3 retrospectives, regarding the side effects of depression in patients using isotretinoin, published between 1984 and 2004, and concluded that there were no causal associations between isotretinoin and depression Webster et al. reported that the symptoms of secondary depression improved gradually even with the continuation of isotretinoin treatment.[24,25]

Recently, in their meta-analysis, Li et al. showed that isotretinoin administration is associated with a reduction in depressive symptoms in patients suffering from acne.[26]

Some researchers arguing that isotretinoin is not associated with depression suggested that the depression after isotretinoin use is coincidental, and that isotretinoin provides a decrease in anxiety and depression symptoms along with an improvement in body image.[12,18-20]

Our results support this argument by showing a significant decrease in BDI scores after isotretinoin treatment. One aspect of our study that contributes to the literature data was that not only depression and anxiety but also symptoms such as somatization, obsession, sensitivity, and anger can be evaluated by using the SCL-90-R Psychological Symptom Screening test, which was not used in previous studies. Similar to BDI and AQOLS, it was found that SCL-90-R somatization, obsession, depression, sensitivity, anger, and general symptom index scores decreased at significant levels after the treatment ($p<0.05$). The fact that the results of all three tests support each other also supports the reality of our conclusion.

Studies speculating that isotretinoin causes depression are mostly case reports, and controlled studies supporting the relationship between isotretinoin and depression are limited.

One of these controlled studies was Azoulay et al. which emphasized that the risk of depression increased threefold after the use of isotretinoin in patients with no history of depression.[27]

However, the number of retrospectives and prospective controlled studies in which no significant relations were detected between isotretinoin and depression in parallel with our study is much higher. Despite this, the presence of publications speculating that depressive symptoms develop during isotretinoin treatment shows that patients must be followed up for the development of depression and psychiatric symptoms during the treatment process.

In their study, Golchai et al. reported no significant relationship between anxiety and depression scores and disease severity.[21] Kubota et al. conducted a study with 859 Japanese adolescents, and reported that patients with acne were more depressed than those without skin problems, female students were more depressed than male students, and those with acne duration longer than 2 years had a higher depression rate than those with less than 6 months.[28]

In the present study, it was found that those with severe acne had higher scores on psychiatric tests than those with moderate acne. Our results reveal the relationship between acne and psychiatric mood and showed that the increase in acne severity increases the negative effect on the psychological state of the patient.

It was reported in some studies that acne increases suicidal ideation. It was also suggested that isotretinoin used in the treatment may cause this.[29] None of the patients included in the present study had suicidal ideation at the beginning of the treatment. No suicidal ideation developed in any of the patients after 6 months of isotretinoin treatment. The data at hand show the possibility that suicidal ideation in patients with acne may be related to the psychological negativity caused by acne, and the fact that no patient with suicidal ideation was faced with isotretinoin treatment also shows that this treatment may not be associated with suicidal ideation. Also, the improvement in the psychological symptoms of our patients with treatment supports this view.

The limitations of the study were that the sample size was small and it was based only on the statements of the patients for systemic diseases, which might affect the psychiatric test results, and no laboratory data were evaluated.

CONCLUSION

It was shown in the present study that isotretinoin treatment does not cause depression and psychological symptoms, and even improves depression and psychological symptoms because of acne and improves the quality of life. When the existing debate on this topic is considered, more studies with larger samples and long follow-ups are needed to evaluate the acute and chronic effects of isotretinoin on mood and the role of time.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Türkan Tuğba Yıldız;* ***Design:*** *Türkan Tuğba Yıldız;* ***Control/Supervision:*** *Türkan Tuğba Yıldız;* ***Data Collection and/or Processing:*** *Türkan Tuğba Yıldız, Mehmet Melikoğlu;* ***Analysis and/or Interpretation:*** *Türkan Tuğba Yıldız, Halil Özcan;* ***Literature Review:*** *Zeynep Utlu, Türkan Tuğba Yıldız;* ***Writing the Article:*** *Türkan Tuğba Yıldız, Zeynep Utlu;* ***Critical Review:*** *Halil Özcan, Mehmet Melikoğlu;* ***References and Fundings:*** *Mehmet Melikoğlu.*

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