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ORIGINAL CONTRIBUTION

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Effects of isotretinoin on the hair cycle

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Abstract

Background/ Objectives: Isotretinoin is a synthetic vitamin A agent that affects all of the pathogenic factors that suppress sebum production and play a role in the formation of acne. It is frequently used in the treatment of moderate-severe acne vulgaris. However, there are some mucocutaneous and systemic side effects that limit the use of isotretinoin. In this study, we aimed to determine the effect of isotretinoin on hair growth parameters.

Material and Methods: Isotretinoin treatment at 0.5 mg/kg per day dose was started to patients with moderate-severe acne vulgaris, and hair growth parameters were evaluated before treatment and after 3 months of treatment. Parameters were measured by Fotofinder dermatoscopy device using the TrichoScan Professional program.

Results: In the TrichoScan analysis, the total hair count, hair density, percentage of anagen and telogen hair, density, count, and ratio of vellus and terminal hairs in the 0.73 area were calculated. As a result, there were differences in some values between the first analysis and the second analysis. However, these differences were not statistically significant.

Conclusion: Our study was based on the mucocutaneous side effects of isotretinoin which are telogen effluvium and thinning hair. Our results support that the drug does not alter hair growth parameters in the short term and when very high doses are not used.

KEYWORDS
acne vulgaris, hair, isotretinoin, telogen effluvium, TrichoScan

1 | INTRODUCTION

Acne vulgaris (AV) is a chronic, multifactorial disease affecting the pilosebase unit.[1] It is thought that 85% of the young population aged between 12-24 years suffer from AV. AV can be occurred all over the world and all races. However, it is more common in white race than black ones.[2] Acne pathophysiology comprises the complex interaction of many internal and external factors on the pilosebase unit. The understanding of the specific structure of pilosebase unit, its microscopic and physiological anatomy, is important to understand the pathogenesis of acne and to establish an effective treatment regimens. Pathophysiological factors which are responsible for disease development can be classified under the four main titles: abnormal follicular keratinization, excessive sebum production, propionibacterium acnes colonization, and inflammation.[3,4] Although acne does not threaten life, it is one of the diseases which are the most affecting the patient's psychosocial status and quality of life. Shame, depression, anxiety, irritability, social isolation, and suicide attempts are more frequent in these patients. All of these affect the quality of life in a negative way.[5]

Isotretinoin is an effective treatment agent that effects on all steps of acne pathogenesis.[6] According to the recent guidelines, isotretinoin should be used in the treatment of moderate-severe acne.[7] It has a wide side effect profile because retinoic acid receptors are present in all parts of the body. The incidence and severity of side effects except for teratogenicity are dose-dependent and reversible

when the drug is stopped. The most common side effects are related to the skin and mucous membranes. At varying degrees, cheilitis is seen in almost all patients. Less frequent side effects are thinning in the hair and telogen effluvium.[8-10] Retinoids cause deterioration of telogen stability and shorten the anagen process. Occasionally, retinoid-related telogen effluvium may cause coincidental androgenetic alopecia and shedding may continue. Acitretin-related alopecia frequency is reported to be 15%-87.5%, etretinate-related alopecia frequency is reported to be 4%-76%, and isotretinoin-related alopecia frequency is reported to be 8%-10%. Dose-dependent diffuse telogen hair loss is commonly found in etretinate and acitretin but less seen in isotretinoin.[11]

TrichoScan is a program frequently used by dermatologists in recent years. TrichoScan Professional was introduced in 2001 as a device that can measure important parameters for hair, such as hair growth and hair loss. It is also a combination of epiluminescence microscope and automatic digital image analysis. The number of hairs in an area, the percentage of hair in anagen or telogen phase, and the terminal and vellus hair percentage are the parameters that can be measured with it.[12,13]

The number of studies showing the effect of isotretinoin on hair is scarcely any. In this study, we planned to look at the effects of drug on the hair growth parameters with TrichoScan program.

Learning points

Mucocutaneous side effects of isotretinoin are well down, but the effect on the hair is not clear. Here, we aimed to find out this by TrichoScan method which shows the best effect of drugs on hair.

2 | MATERIAL AND METHODS

Local ethics committee approved our study that it is compatible with provisions of the declaration of Helsinki. We included 30 consecutive patients who were admitted to the polyclinic with diagnosis of nodulocystic or scarring acne complaints. Informed consent form was obtained from all participants. Patients with psychiatric disorder, another chronic disease, drug hypersensitivity, and pregnant/lactating female patients were not included to study. Patients outside the specified age range also excluded.

Systemic isotretinoin treatment was planned for these patients. They were informed about the medication and the treatment to be performed. The patients were examined before the isotretinoin treatment (initial and monthly regular liver function tests, blood lipids, fasting glucose, and β-HCG value for pregnancy in female patients). Thirty patients who wanted to participate were selected by giving information about the study to be performed. Necessary informations were recorded to data entry form such as patient's name and surname, phone, age, duration of acne, previous medications, patient's history, family history, systemic diseases, laboratory tests, condition of hair loss, and grade of acne vulgaris. Isotretinoin treatment at 0.5 mg/kg per day to all patients has begun. The treatment was continued until the cumulative dose reached to 120-150 mg/kg about 6-7 months. Before starting the medication and at the end of the third month, TrichoScan was performed with digital dermoscope. The hair in the temporoparietal and occipital regions of all patients was cut with a shaving machine to a thickness of 0.5 mm in the 1 cm^2 area. We measured from the same area in all patients because of the consistency of results and the opportunity to accurately follow changes in the same area over time. Another reason to use this area was to protect against the false results of androgen exposure in male patients. The patients were recalled after 3 days after cutting. When the patients came, the cut area was painted with black dye mixed with special solution. The dye was kept in the patient's hair for 12-15 minutes. After cleaning the dyed area with a special alcohol solution, the photo was taken by Fotofinder Videodermoscope (FotoFinder Systems GmbH, Bad Birnbach, Germany) at 30 magnification while the floor was still wet. This photo, which was transferred to a computer environment, was analyzed with the TrichoScan software program, and the results were obtained.

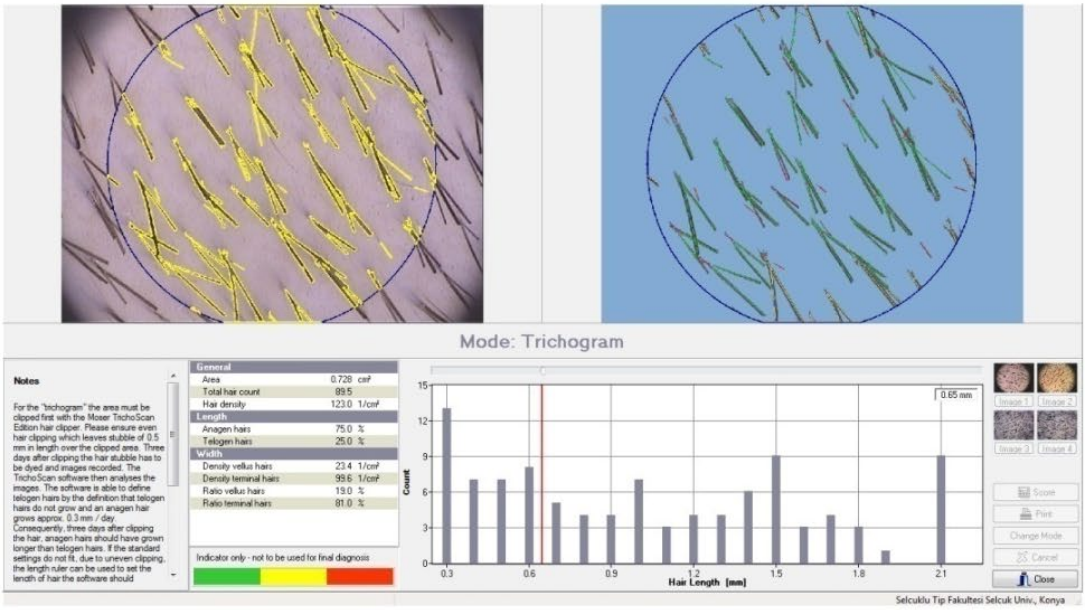
A total of 0.7 cm^2 of the shaved 1 cm^2 area was analyzed with TrichoScan. Non-growing hair was red and telogen, growing hair was green and anagen, and yellow hair was evaluated as end-of-cycle hair. In the analysis of 0.7 cm^2 area, the total number of hair, the density of the hair, anagen hair, telogen hair, density of the vellus and the terminal hair, the number, and the ratio were obtained (Figure 1).

The data obtained in the study were analyzed via SPSS (Statistical Package for Social Sciences) for Windows 22.0 program (IBM, Armonk, NY, USA). Number, percentage, mean, and standard deviation were used as descriptive statistical methods in the evaluation of the data. "Paired-Samples *t* test" was used to compare the changes in pre-treatment period and 3rd month of treatment. SPSS (ver: 13) (IBM, Armonk, NY, USA) statistical package program was used for the analysis. *P* value < 0.05 was accepted as the criterion for statistical significance.

3 | RESULTS

Thirty patients diagnosed with severe acne vulgaris included to study. The descriptive features of the patients are summarized in Table 1.

Examined hair parameters show minimal changes between the first and second analyzes. In the first analysis, the total hair count was 176 314 ± 5314, in the second analysis 177 248 ± 5874; in the first analysis, hair density was 242 154 ± 9475, in the second analysis 243 987 ± 10 147; the percentage of telogen hair was 33.26 ± 11.75, in the second analysis 31.58 ± 11.08; the density of vellus hair was 36.68 ± 13.74 in the first analysis, 40.97 ± 14.10 in the second analysis; the count of vellus hair was 26.68 ± 9.99 in the first analysis and 29.81 ± 10.26 in the second analysis. However, it was not statistically significant because *P* values were >0.05. The changes between the pre-treatment period and end of 3rd month of treatment are shown in Table 2 and Figure 2.



Trichogram

Area [cm²]	0.73
Total hair count	89.5
Hair density [1/cm²]	123.0
Anagen hairs [%]	75.0
Telogen hairs [%]	25.0
Density vellus hairs [1/cm²]	23.4
Density terminal hairs [1/cm²]	99.6
Count vellus	17.0
Count terminal	72.5
Ratio vellus hairs [%]	19.0
Ratio terminal hairs [%]	81.0

FIGURE 1 An example of TrichoScan

4 | DISCUSSION

Isotretinoin is a retinoic acid-derived treatment agent that is recently used successfully in the treatment of nodulocystic acne.[9] Isotretinoin reverses the factors that are effective in the pathogenesis of acne, directly or indirectly. Mucocutaneous effects, the most common side effect of isotretinoin therapy, are dose-dependent and reversible.[14] Skin and mucous membrane lesions develop in almost all patients when the drug is used at higher doses than 0.5 mg/kg per day.[15]

Many drugs have been associated with hair loss, but only a group of them cause telogen effluvium. In the Physician's Desk Reference database, 295 different agents were identified for alopecia. The most frequently blamed agents are anticonvulsants (such as phenytoin, valproic acid, carbamazepine), antithyroid drugs (such as propylthiouracil, methimazole), anticoagulants (especially heparin), and β-adrenergic blockers (such as propranolol). Retinoids are also among the drugs that cause hair loss. Retinoids cause deterioration of telogen stability and decrease in the anagen process, which can lead to diffuse or localized (telogen effluvium) hair loss during treatment. This effect is more common in acitretin than isotretinoin. Studies have shown that objective alopecia occurs at high doses.[16,17] In our study, we observed that isotretinoin at 0.5 mg/kg per day doses did not affect the hair parameters within 3 months and patients did not complaint from alopecia.

Pilosebase unit consists of hair follicle and sebaceous gland and needs a certain level of retinoic acid. Retinoic acid synthesis occurs in the stem cells located on pilosebase unit. The mechanism of retinoic acid is not fully known in here. Vitamin A, at normal levels, is necessary to fulfill the optimal functions of hair follicle and sebaceous unit. However, in case of toxicity, hair loss is inevitable. Vitamin A toxicity also reduces sebaceous gland function and is used in the treatment of acne. Studies conducted with mouse models support the role of retinoic acid in the hair follicle. In these studies, decreased retinoic acid signals and increased levels of retinol and all-trans retinoic acid (ATRA) in the basal layer and outer root sheath lead to progressive hair loss. Retinoic acid signal retention is delaying the onset of the anagen phase, and the increase in retinol and ATRA facilitates the passage to anagen from the telogen phase. Again in mouse models, retinoid X receptors (RXR) have been found to associate with many nuclear receptors and vitamin D receptors (VDR). Although it does not seem possible, it is mentioned that the reduction in ATRA levels leads to a change in vitamin D metabolism and signaling, and the replacement of this reduced vitamin A with diet leads to improvement in vitamin D metabolism and signaling.[18] In a study, those findings have shown; vitamin D plays an important role in the proliferation and differentiation of keratinocytes and in the initiation of anagen phase in hair cycle; mice with deletions in RXR receptors have developed alopecia similar to mice without VDR; and RXR-VDR heterodimerization is necessary for postnatal hair cycle. Again, in the same study, although hair loss was commonly seen during oral retinoid use, they are talking about the fact that this mechanism has not been fully understood.[19]

In the literature, the number of prospective studies that determine the effect of isotretinoin on hair is scarce. In a study similar to ours, biophysical skin parameters and hair growth parameters were examined before and after treatment with isotretinoin for 5-7 months at 0.5-1 mg/kg per day. Reduced anagen hair ratio in their patients may cause telogen effluvium hair loss.[20]

Drugs have many side effects on the hair. Most common side effect is hair loss. In addition to this, color and structure changes are rarely seen. Seckin et al in 2009 detected a 70-year-old patient who used acitretin for the treatment of psoriasis, had blackening, and curling in the hair on the occipital region after 6 months of treatment. Acitretin is believed to cause this because it affects the inner root sheath and deteriorates the keratinization. Same color and structural changes were previously observed also in the etretinate, but no such side effects have been reported with isotretinoin.[21] We also have not encountered any color or structural change in our work.

TrichoScan is an easy, fast, and cheap method that can be used to compare treatments with placebo, to compare different substances that promote hair growth, to identify androgenetic alopecia (AGA) and other hair loss, to investigate the effects of various drugs on hair, and to determine the effects of laser treatments on hypertrichosis and hirsutism.[22] The number of studies conducted to investigate the effects of drugs on the hair in the past is very few, and most of them are associated with AGA.

In the literature, isotretinoin has been reported to cause telogen effluvium by disturbing telogen stability.[20] But our patients did not clinically describe hair loss after the third month of the drug. TrichoScan showed changes of isotretinoin on the total hair count, hair density, percentage of telogen hair, density of vellus hair, and count of vellus hair which were not statistically significant. We found that isotretinoin

TABLE 1 Demographic features of patients with acne vulgaris

Gender	Females	19	63 333
	Males	11	36 667
	Total	30	100
	Min-Max	**Mean**	**SD**
Age	18-27	21 530	2112

TABLE 2 Comparison hair growth parameters before and at the end of the third month of treatment

		Before		After		
	n	Mean	SD	Mean	SD	*P*
Total hair count	30	176 314	5314	177 248	5874	0.597
Hair density	30	242 154	9475	243 987	10 147	0.602
Anagen hairs (%)	30	66 740	13 248	68 418	14 245	0.148
Telogen hairs (%)	30	33 260	11 751	31 582	11 083	0.148

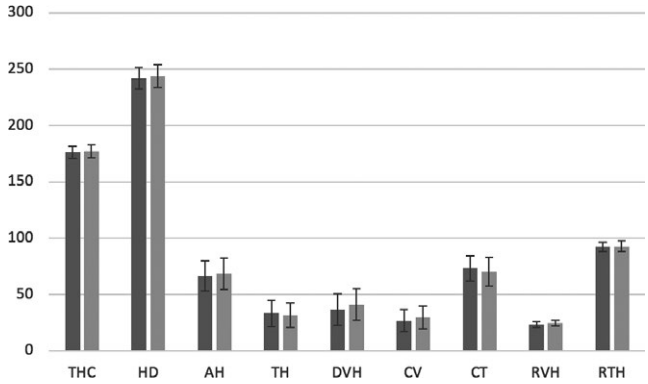


FIGURE 2 Comparison of all hair growth parameters of patients. AH, Anagen hair; CT, Count terminal; CV, Count vellus; DVH, Density vellus hair; HD, Hair density; RTH, Ratio terminal hairs; RVH, Ratio vellus hairs; TH, Telogen hair; THC, Total hair count

did not affect the hair parameters and did not cause to telogen effluvium at low doses and in short term according to our study. We can say that TrichoScan is an easy and noninvasive method that can be applied in polyclinics; there are also some disadvantages as well, such as requirement of time and effort, need for patients to come and appeal more than once to polyclinics. Because of this, the number of studies with TrichoScan is very few and there are insufficiencies in comparison and supporting the differential diagnosis. Our study is one of the few studies conducted to investigate the effects of isotretinoin on hair. According to our data, isotretinoin can be planned low doses and short term when we suffer from hair loss in a group of patient.

The results of our study should be evaluated in light of its limitations. One of the main limitations of this study was TrichoScan was not performed at the end of treatment course, due to our afraid of patients leave the treatment. Since the effects of isotretinoin are directly related to the cumulative dose, different results might appear if the TrichoScan was repeated at the end of treatment course. Another limitation was small sample size which prevented us from obtaining definitive findings about TrichoScan analyses and hair loss. And last limitation of us, isotretinoin was not administered at high doses. Future studies with higher number of cases, high doses, and long-term administration will help to understand the effects of drug on the hair better.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTION

All authors have contributed significantly.

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