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A.Abdelmaksoud put the concept, reviewed the literature, wrote the initial draft, and submitted the final draft. S.Temiz, R.Dursun, and B.Işık reviewed and followed up the cases, and analyzed their data. S.Temiz and M.Vestita shared in literature review. U. Wollina reviewed and edited the initial draft. L.Rudnicka and T.Lotti revised and edited the final draft. All the authors approved the final draft for submission.

Isotretinoin-induced Hair disorders in the Era of COVID-19 and Related vaccines: A case series

Dear Editor,

Acne vulgaris is a common disease of teenagers that may continue until adulthood. Isotretinoin (ISO) (13-cis retinoic acid) is the most renewed treatment for moderate-to-severe acne. ISO should be introduced precociously for mild-to-moderate acne not responding to conventional therapy, if there is no formal contraindication.[1,2] ISO has dose-dependent side effects, which are secondary to retinoic acid receptors expression in the tissues. These side effects are reversible with drug discontinuation. ISO-induced dryness of the skin and mucocutaneous membranes is the common known side effect.[3] Data on ISO-related hair disorders are limited in the literature, even in the era of COVID-19 and related vaccines.

Herein, we have reported acne patients on ISO in two hospitals in Turkey presented with hair disorders between December 2020 and March 2022 ***(Figure-1 &Table-1).*** The patients were otherwise healthy 21 females, with a mean age of 20 years, who were on ISO for acne vulgaris (7 mild, 8 moderate, and 4 severe degrees, according to The Global Acne Scarring Grading System[4]) presented with hirsutism (6) or telogen effluvium (TE) (15) during the course of ISO. None of hirsute patients had history of menses irregularities, polycystic ovary syndrome (PCOS), or on anti-androgenic therapy. The dose range of ISO was 0.25-0.5 mg/kg/day. The average cumulative dose was 2543 mg. The mean duration of ISO course at time of presentation was 11.8 weeks. The mean time of onset of hair disorders was 6.9 weeks. Five patients had history of pauci-symptomatic, PCR-confirmed COVID-19 prior to presentation. The average duration of COVID-19 symptoms was 2,2 weeks. For those with COVID-19 history, ISO commenced after 1 month of recovery in 1 case, and after 6 months in five. Five cases had prior history of COVID-19 vaccination, one of them in the second month of ISO (case 16). None of the patients had discontinued ISO. The mean time of recovery for TE was 5.2 weeks. Follow up is being for hirsute patients.

Hair loss in the form of TE is a reported side effect of ISO that can lead to treatment discontinuation. Retinoids are possibly arrest the onset of the anagen phase of the hair

cycle and impair the anchoring of hair during the telogen phase, ultimately increasing hair shedding.[5] In a study by Hull et al. on 124 adolescents and adults using ISO for acne, it was reported that hair loss increased from 7% in the fourth month of treatment to 14% at the end of treatment.[6] İslamoğlu et al. noted that ISO in low doses and short courses of therapy did not affect hair parameters or lead to TE.[7] Lytvynet al. reported that patients on < 0.5 mg/kg/d of ISO experienced hair loss at a frequency of 3.2% versus those on ≥0.5 mg/kg/d, who experienced hair loss at a frequency of 5.7%. The authors suggested low-dose ISO as an alternative approach to drug discontinuation.[3] Aksac et al. noted that addition of 10 mg/day biotin to ISO has increased the rate of anagen hair and reduced the rate of telogen hair, eventually could help in lessening the risk of ISO-induced hair loss.[8]

COVID-19- associated TE (CATE), a form of hair loss developed several weeks after recovery from COVID-19, is estimated to occur in up to 60% of SARS-CoV-2 infected patients. Therefore, exclusion of COVID-19 history is important in any patient presented with hair loss and has been diagnosed with TE.[9] CATE is expected to resolve spontaneously within 1-6 months of onset. However, minoxidil, finasteride, and topical clobetasol may be required.10 Of interest; TE has been recently reported 5 weeks after the first dose of ChAdOx1 nCoV-19 Corona virus recombinant vaccine (Covishield).[11] On the other hand, hirsutism is one of the possible side effects of ISO therapy that may be transient or take several months to resolve on drug discontinuation.[12] Hirsutism is often associated with hyperandrogenemia. However, half of the patients with mild symptoms have normal androgen levels.[12] Aktar et al. noted that the risk of hirsutism secondary to ISO is mostly related to peripheral increased sensitivity of androgen receptors to ISO with no associated change in the level of androgen hormones.[13] That may explain why ISO-induced hirsutism reports were not associated with additional signs of hyperandrogenism.[12] In addition to Aktar et al's results, Akpolat reported that ISO could decrease sex hormone-binding globulin (SHBG) level and increase levels of circulating free testosterone, total testosterone, and dehydroepiandrosterone sulfate (DHEAS) leading to an increase in Ferriman-Gallwey (FG) hirsutism score.[14] A 3-month course of ISO is sufficient to increase the risk of FG hirsutism score. Higher FG scores could be expected on longer courses.[13] We noted a significant hirsutism score as short as 2 weeks of ISO commencement in our patients.

In summary, we noted that ISO-induced TE is transient and improved spontaneously even without drug discontinuation. A dose reduction of ISO should be considered in those patients who are concerned about hair loss, those who had recent history of COVID-19 or recently vaccinated for COVID-19.[3,9,11] Further studies on larger number of patients are warranted to reach the precise pathomechanism of ISO-induced hair disorders.

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Figure Legends:

Figure 1: Onset and recovery time of ISO-induced telogen effluvium.

Table 1: Isotretinoin-induced hair disorders.

Patient	Age (Year)	Sex	Hair disorder ***MFGSI***	Acne degree	ISO Cumulative dose (mg)	Treatment duration of ISO (week)	History of COVID-19infection **Or** COVID-19 vaccination	COVID-19 systemic symptoms	Onset of hair disorder after ISO treatment (week)	Recovery time of hair disorder (week)
1	14	F	H/10	Mild	1800	9	None	-	6	Pending
2	34	F	H/16	Moderate	5100	14	***YES**** ^Sinovac-CoronaVac ***(three doses)***	Sore throat, mild fever	8	Pending
3	21	F	H/14	Severe	300	2	None	-	2	Pending
4	17	F	H/10	Mild	1500	8	None	-	6	Pending
5	15	F	H/8	Moderate	4200	22	None	-	10	Pending
6	16	F	H/12	Severe	1800	8	None	-	6	Pending
7	18	F	TE	Severe	600	4	None	-	4	6
8	19	F	TE	Mild	2400	14	None	-	8	6
9	22	F	TE	Moderate	1200	8	***YES****	Fatigue, Muscle aches	8	10
10	16	F	TE	Mild	6900	36	None	-	12	10
11	23	F	TE	Moderate	3300	10	***YES****	Fatigue, Muscle aches	10	8
12	17	F	TE	Mild	3600	16	None	-	8	6
13	20	F	TE	Moderate	300	2	None	-	2	6

14	35	F	TE	Mild	1500	8	***YES*** ** ^Pfizer-BioNTech ***(two doses)***	Mild fever	6	8
15	19	F	TE	Moderate	4200	22	None	-	12	8
16	21	F	TE	Severe	1800	8	***None*** ^Pfizer-BioNTech ***(two doses)***	-	8	8
17	18	F	TE	Mild	600	4	None	-	4	6
18	19	F	TE	Moderate	2400	14	***None*** ^Pfizer-BioNTech ***(two doses)***	-	8	6
19	17	F	TE	Mild	2700	12	***YES*** **	Sore throat	6	8
20	17	F	TE	Moderate	2400	9	None	-	6	8
21	22	F	TE	Moderate	4800	17	***None*** ^Sinovac-CoronaVac ***(three doses)***	-	6	6

Table 1: Isotretinoin-induced Hair Disorders.

F: Female. **H:** Hirsutism. **TE:** Telogen effluvium (*diagnosed based on history and trichospoic examination*). **MFGSI:** *Modified Ferriman Galleyway Severity Index*.

** Prior PCR-confirmed diagnosis of COVID-19, no other mucocutaneous signs, no pulmonary involvement, received symptomatic therapy, ISO commenced 1 month and 6 months of recovery in case number 19, and in the others, respectively. None had additional hyper-androgenic sings. Follow up is being.

^ Had received COVID-19 vaccination; 3 received two doses of *Pfizer-BioNTech* COVID-19 Vaccine (COMIRNATY)& two received 3 doses of *Sinovac-CoronaVac* COVID-19 vaccine. Case number 16: within the second month of ISO therapy, while 1-6 months prior to ISO therapy for the others.