Letters to the Editor

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 and 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. 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 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 Lytvyn et 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. 8 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,
| Patient | Age (Year) | Sex | MFGSI | Acne degree | ISO Cumulative dose (mg) | Treatment duration of ISO (week) | Hair disorder | History of COVID-19 infection 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                              | None           | YES<sup>a</sup> 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<sup>a</sup> | Fatigue, Muscle aches                        | —                               | 8                                        | 10                                       |
| 10      | 16         | F   | TE    | Mild        | 6900                     | 36                              | None           | —                                             | —                               | 12                                       | 10                                       |
| 11      | 23         | F   | TE    | Moderate    | 3300                     | 10                              | YES<sup>a</sup> | 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<sup>a</sup> Pfizer-BioNTech (two doses) | Mild fever     | —                                             | —                                        | 6                                        |
| 15      | 19         | F   | TE    | Moderate    | 4200                     | 22                              | None           | —                                             | —                               | 12                                       | 8                                        |
| 16      | 21         | F   | TE    | Severe      | 1800                     | 8                               | None           | YES<sup>b</sup> Pfizer-BioNTech (two doses)  | —                               | 8                                        | 8                                        |
| 17      | 18         | F   | TE    | Mild        | 600                      | 4                               | None           | —                                             | —                               | 4                                        | 6                                        |
| 18      | 19         | F   | TE    | Moderate    | 2400                     | 14                              | None           | YES<sup>b</sup> Pfizer-BioNTech (two doses)  | —                               | 8                                        | 6                                        |
| 19      | 17         | F   | TE    | Mild        | 2700                     | 12                              | YES<sup>a</sup> | Sore throat                                  | —                               | 6                                        | 8                                        |
| 20      | 17         | F   | TE    | Moderate    | 2400                     | 9                               | None           | —                                             | —                               | 6                                        | 8                                        |
| 21      | 22         | F   | TE    | Moderate    | 4800                     | 17                              | None           | YES<sup>b</sup> Sinovac-CoronaVac (three doses) | —                               | 6                                        | 6                                        |

Abbreviations: F, Female; H, Hirsutism; MFGSI, Modified Ferriman-Galleyway Severity Index; TE, Telogen effluvium (diagnosed based on history and trichoscopic examination).

<sup>a</sup>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 signs. Follow up is pending.

<sup>b</sup>Had received COVID-19 vaccination; 3 received two doses of Pfizer-BioNTech COVID-19 Vaccine (COMIRNATY) and 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.
finasteride, and topical clobetasol may be required. Of interest; TE has been recently reported 5 weeks after the first dose of ChAdOx1 nCOV-19 Corona virus recombinant vaccine (Covishield). 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. Hirsutism is often associated with hyperandrogenemia. However, half of the patients with mild symptoms have normal androgen levels. Akter 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. That may explain why ISO-induced hirsutism reports were not associated with additional signs of hyperandrogenism. In addition to Akter 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. 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. 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. Further studies on larger number of patients are warranted to reach the precise pathomechanism of ISO-induced hair disorders.

AUTHOR CONTRIBUTIONS
Abdelmaksoud conceived 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.

CONFLICT OF INTEREST
None to declare.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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